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# THE UNITED STATES OF AMERICA

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United States Patent and Trademark Office

December 06, 2004

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APPLICATION NUMBER: *60/532,849*
FILING DATE: *December 24, 2003*

**PRIORITY DOCUMENT**
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PTO/SB/16 (06-03)
Approved for use through 07/31/2003. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE


00727 U.S. PTO 60/532849 122403

# PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

**Express Mail Label No.** EL614836744US

## INVENTOR(S)

| Given Name (first and middle [if any]) | Family Name or Surname | Residence (City and either State or Foreign Country) |
|---|---|---|
| Manpreet Vick S. | Wadhwa | |

☐ *Additional inventors are being named on the ____ separately numbered sheets attached hereto*

## TITLE OF THE INVENTION (500 characters max)

Compounds Useful For Treating Cox-2 Mediated Conditions

## CORRESPONDENCE ADDRESS

*Direct all correspondence to:*

☒ Customer Number **26,648**

*OR*

| | | | | | |
|---|---|---|---|---|---|
| ☐ Firm or Individual Name | | | | | |
| Address | | | | | |
| Address | | | | | |
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| Country | | Telephone | | Fax | |

## ENCLOSED APPLICATION PARTS *(check all that apply)*

☒ Specification *Number of Pages* 47

☒ Drawing(s) *Number of Sheets* 10

☐ Application Data Sheet. See 37 CFR 1.76

☐ CD(s), Number

☐ Other (specify)

## METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT

☐ Applicant claims small entity status. See 37 CFR 1.27.

☐ A check or money order is enclosed to cover the filing fees

☒ The Director is hereby authorized to charge filing fees or credit any overpayment to Deposit Account Number 19-1025

☐ Payment by credit card. Form PTO-2038 is attached.

FILING FEE AMOUNT ($) **$160.00**

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☒ No.

☐ Yes, the name of the U.S. Government agency and the Government contract number are: ____________

*Respectfully submitted,*

SIGNATURE Kenton N. Fedde

Date 24-Dec 03

TYPED or PRINTED NAME Kenton N. Fedde

REGISTRATION NO. 54,701
*(if appropriate)*

Docket Number: 00931/PR/US

TELEPHONE 314-274-5402

## USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

Approved for use through 04/30/2003. OMB 0651-0032
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE


# FEE TRANSMITTAL for FY 2003

*Effective 01/01/2003. Patent fees are subject to annual revision.*

☐ Applicant claims small entity status. See 37 CFR 1.27

**TOTAL AMOUNT OF PAYMENT** ($) $160.00

| Complete if Known | |
|---|---|
| Application Number | TBA |
| Filing Date | |
| First Named Inventor | Manpreet Vick S. Wadhwa |
| Examiner Name | TBA |
| Group Art Unit | TBA |
| Attorney Docket No. | 00931/PR/US |

## METHOD OF PAYMENT *(check all that apply)*

☐ Check ☐ Credit card ☐ Money Order ☐ Other ☐ None

☒ Deposit Account:

Deposit Account Number: 19-1025

Deposit Account Name: Pharmacia Corporation

The Director is authorized to: *(check all that apply)*

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☒ Charge any additonal fee(s) during the pendency of this application

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## FEE CALCULATION

### 1. BASIC FILING FEE

| Large Entity Fee Code | Large Entity Fee ($) | Small Entity Fee Code | Small Entity Fee ($) | Fee Description | Fee Paid |
|---|---|---|---|---|---|
| 1001 | 750 | 2001 | 375 | Utility filing fee | |
| 1002 | 330 | 2002 | 165 | Design filing | |
| 1003 | 520 | 2003 | 260 | Plant filing fee | |
| 1004 | 750 | 2004 | 375 | Reissue filing | |
| 1005 | 160 | 2005 | 80 | Provisional filing fee | 160.00 |

SUBTOTAL (1) ($) $160.00

### 2. EXTRA CLAIM FEES FOR UTILITY AND

| | Extra Claims | | | Fee from below | | Fee Paid |
|---|---|---|---|---|---|---|
| Total Claims | | -20** = | 0 | X | = | 0.00 |
| Independent Claims | | - 3** = | 0 | X | = | 0.00 |
| Multiple Dependent | | | | | = | |

| Large Entity Fee Code | Large Entity Fee ($) | Small Entity Fee Code | Small Entity Fee ($) | Fee Description |
|---|---|---|---|---|
| 1202 | 18 | 2202 | 9 | Claims in excess of 20 |
| 1201 | 84 | 2201 | 42 | Independent claims in excess of 3 |
| 1203 | 280 | 2203 | 140 | Multiple dependent claim, if not paid |
| 1204 | 84 | 2204 | 42 | ** Reissue independent claims over original patent |
| 1205 | 18 | 2205 | 9 | ** Reissue claims in excess of 20 and over original patent |

SUBTOTAL (2) ($) $0.00

***or number previously paid, if greater; For Reissues, see above*

## FEE CALCULATION (continued)

### 3. ADDITIONAL FEES

| Large Entity Fee Code | Large Entity Fee ($) | Small Entity Fee Code | Small Entity Fee ($) | Fee Description | Fee Paid |
|---|---|---|---|---|---|
| 1051 | 130 | 2051 | 65 | Surcharge - late filing fee or oath | |
| 1052 | 50 | 2052 | 25 | Surcharge - late provisional filing fee or cover sheet | |
| 1053 | 130 | 1053 | 130 | Non - English specification | |
| 1812 | 2,520 | 1812 | 2,520 | For filing a request for *ex parte* reexamination | |
| 1804 | 920* | 1804 | 920* | Requesting publication of SIR prior to Examiner action | |
| 1805 | 1,840* | 1805 | 1,840* | Requesting publication of SIR after Examiner action | |
| 1251 | 110 | 2251 | 55 | Extension for reply within first month | |
| 1252 | 410 | 2252 | 205 | Extension for reply within second month | |
| 1253 | 930 | 2253 | 465 | Extension for reply within third month | |
| 1254 | 1,450 | 2254 | 725 | Extension for reply within fourth month | |
| 1255 | 1,970 | 2255 | 985 | Extension for reply within fifth month | |
| 1401 | 320 | 2401 | 160 | Notice of Appeal | |
| 1402 | 320 | 2402 | 160 | Filing a brief in support of an appeal | |
| 1403 | 280 | 2403 | 140 | Request for oral hearing | |
| 1451 | 1,510 | 1451 | 1,510 | Petition to institute a public use proceeding | |
| 1452 | 110 | 2452 | 55 | Petition to revive - unavoidable | |
| 1453 | 1,300 | 2453 | 650 | Petition to revive - unintentional | |
| 1501 | 1,300 | 2501 | 650 | Utility issue fee (or reissue) | |
| 1502 | 470 | 2502 | 235 | Design issue fee | |
| 1503 | 630 | 2503 | 315 | Plant issue fee | |
| 1460 | 130 | 1460 | 130 | Petitions to the Commissioner | |
| 1807 | 50 | 1807 | 50 | Processing fee under 37 CFR § 1.17(q) | |
| 1806 | 180 | 1806 | 180 | Submission of Information Disclosure Statement | |
| 8021 | 40 | 8021 | 40 | Recording each patent assignment per property (times number of properties) | |
| 1809 | 750 | 2809 | 375 | Filing a submission after final rejection (37 CFR § 1.129(a)) | |
| 1810 | 750 | 2810 | 375 | For each additional invention to be examined (37 CFR § 1.129(b)) | |
| 1801 | 750 | 2801 | 375 | Request for Continued Examination (RCE) | |
| 1802 | 900 | 1802 | 900 | Request for expedited examination of a design application | |

Other fee (specify) ________________

*Reduced by Basic Filing Fee Paid

SUBTOTAL (3) ($)

| SUBMITTED BY | | | | Complete *(if applicable)* | |
|---|---|---|---|---|---|
| Name *(Print/Type)* | Kenton N. Fedde | Registration No. *(Attorney/Agent)* | 54,701 | Telephone | 314-274-5402 |
| Signature | Kenton Fedde | | | Date | 24 Dec 03 |

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| **CERTIFICATE OF MAILING BY "EXPRESS MAIL" (37 CFR 1.10)**<br>Applicant(s): **Manpreet Vick S. Wadhwa** | | | Docket No.<br>**00931/PR/US** |
|---|---|---|---|
| Serial No.<br>**TBA** | Filing Date<br>24 Dec 2003 | Examiner<br>**TBA** | Group Art Unit<br>**TBA** |

Invention: **Compounds Useful For Treating Cox-2 Mediated Conditions**

I hereby certify that the following correspondence:

**Fee Transmittal; Provisional Patent Application Cover Sheet; Provisional Patent Application; Itemized Postcard**

***(Identify type of correspondence)***

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**Kenton N. Fedde**
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P06A/REV02

PATENT

(00931/1)

# UNITED STATES PROVISIONAL PATENT APPLICATION

for

# COMPOUNDS USEFUL FOR TREATING COX-2 MEDIATED CONDITIONS

by:

Manpreet Vick S. Wadhwa

**EXPRESS MAIL MAILING LABEL**

NUMBER EL614836744US

DATE OF DEPOSIT 24 December 2003

I hereby certify that this Patent Application is being deposited with the United States Postal Service "EXPRESS MAIL POST OFFICE TO ADDRESSEE" service under 37 C.F.R. §1.10 on the date indicated above and is addressed to:
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Signature Kenton N. Fedde

Kenton N. Fedde

## FIELD OF THE INVENTION

**[0001]** The instant invention relates to cyclooxygenase-2 inhibitory drugs, to pharmaceutical compositions containing such drugs as an active ingredient, to processes for preparing such drugs and compositions, to methods of treatment of cyclooxygenase-2 mediated disorders comprising administering such compositions to a subject, and to the use of such compositions in the manufacture of medicaments.

## BACKGROUND

**[0002]** The discovery of selective COX-2 inhibitory compounds has greatly advanced the treatment and/or prophylaxis of conditions in which COX-2 expression modulates such pathology. Such inhibitory compounds provide anti-inflammatory, antipyretic, analgesic and other useful therapeutic effects while minimizing or eliminating adverse side effects known to result from COX-1 inhibition.

**[0003]** Examples of selective COX-2 inhibitory drugs are set forth in U.S. Patent No. 5,466,823 to Talley *et al* (incorporated herein by reference).

**[0004]** Other examples of selective COX-2 inhibitory drugs are set forth in U.S. Patent No. 5,892,053 to Zhi and Newaz (incorporated herein by reference).

**[0005]** One such example is celecoxib, also known as 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (I). Celecoxib has a therapeutically and prophylactically useful selective COX-2 inhibitory effect, and has utility in treatment and prevention of COX-2 mediated disorder.

**[0006]** International Patent Publication No. WO 00/32189, incorporated herein by reference, discloses that celecoxib has a crystal morphology which tends to form long, cohesive needles. International Patent Publication No. WO 00/42021, incorporated herein by reference, discloses a solvated crystalline form of celecoxib and a method for desolvation of that crystalline form. The forms of celecoxib generally have a low solubility in aqueous media (about 2 to about 5 μg/ml).

**[0007]** Valdecoxib, disclosed in U.S. Patent No. 5,633,272 (incorporated herein by reference), is among another class of selective COX-2 inhibitory drugs. Valdecoxib is practically water insoluble.

[0008] Parecoxib (i.e. N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide) is a valdecoxib pro-drug and is disclosed in U.S. Patent No. 5,932,598 to Talley *et al.*, incorporated herein by reference. Typifying a prodrug, parecoxib shows only very low *in vitro* inhibitory activity against COX-1 and COX-2 but upon administration, parecoxib is converted to the active selective COX-2 inhibitor valdecoxib. Parecoxib sodium, also disclosed in Talley et al., is highly water soluble (e.g. 18 mg/ml at pH 7.8) whereas parecoxib free acid is much less soluble.

[0009] Due to the water solubility of sodium parecoxib, a ready-to-use injectable formulation has been developed and commercialized as Dynastat®. After intravenous injection of such a formulation, parecoxib rapidly becomes bioavailable. Due to the combined effects of (1) rapid bioavailability and (2) *in vivo* clearance of parecoxib, repeated injections at regular intervals (e.g. daily) are required to maintain maximum effectiveness of parecoxib over the course of treatment.

[00010] Parenteral drug formulations have become a very important component in the arsenal of available drug delivery options, particularly for drugs having analgesic effect. For a wide variety of drugs, parenteral routes of administration (e.g. subcutaneous, intramuscular and intravenous injection), offer numerous benefits over oral delivery. For example, parenteral administration of a drug typically results in attainment of a therapeutically effective blood serum concentration of the drug in a shorter time than is achievable by oral administration. This is especially true of intravenous injection, whereby the drug is placed directly in the bloodstream. Whereas orally ingested drugs tend to result in variable losses in the gastrointestinal tract (e.g. due to metabolism, binding to food and other causes), parenteral administration can result in more predictable blood serum concentrations of a drug. For similar reasons, parenteral administration often permits dose reduction. Parenteral administration is generally the preferred method of drug delivery in emergency situations, and is also useful in treating subjects who are uncooperative, unconscious, or otherwise unable or unwilling to accept oral medication.

[00011] It is often desired that a parental drug formulation would provide for a longer action, thereby reducing the frequency of administration. This is especially true when the parental route of administration is invasive painful, emotionally

stressful, associated with risk of infection, or requiring of a visit to a health care provider.

**[00012]** The healing arts would be advanced if a new parecoxib compound could be invented that, when properly formulated, would be useful for a long acting medicament and thereby reduce the number of injections or the difficulties associated with oral medications in certain situations.

## BRIEF SUMMARY OF THE INVENTION

**[00013]** There is now provided in the instant invention a selective COX-2 inhibitory compound comprising a magnesium salt of parecoxib useful for treating a subject with a COX-2 mediated disorder.

**[00014]** It should be understood that the term "treating a subject with a COX-2 mediated disorder" is mean to embrace prophylactic administration of the instant compound to a subject with a likelihood of developing a COX-2 mediated disorder. Also, as used herein, the term "COX-2 mediated disorder" is meant to embrace conditions where COX-2 activity underlies a pathology or an unwelcomed physical effect.

**[00015]** In one embodiment, the magnesium salt of parecoxib is magnesium diparecoxib.

**[00016]** In one embodiment, the magnesium diparecoxib of the present invention is crystalline. In another embodiment, the magnesium diparecoxib crystals are non-needle-like. By way of example, the non-needle-like crystals of the present invention are cuboidal or polygonal.

**[00017]** In another embodiment, magnesium diparecoxib of the present invention is in a pharmaceutically acceptable dosage form. Such dosage forms are useful for oral ingestion as a tablet, capsule, suspension, and the like.

**[00018]** In another embodiment, the pharmaceutically acceptable dosage form of the instant invention is a composition suitable for parenteral administration.

**[00019]** In another embodiment, the parenterally administrable composition of the instant invention is suitable for depot administration.

[00020] In another embodiment, magnesium diparecoxib is in the form of a pharmaceutical dosage form that also contains a second active ingredient.

[00021] In another embodiment, the instant invention provides a depot formulation of a parecoxib salt that, when administered as a depot, results in therapeutic levels of valdecoxib. Such a parecoxib salt is selected from Mg diparecoxib, Zn diparecoxib, Ca diparecoxib, K parecoxib, and Na parecoxib.

[00022] In another embodiment, the instant invention provides a depot composition of valdecoxib that, when administered as a depot to a subject in need thereof, results in therapeutic levels of valdecoxib.

[00023] In another embodiment, a depot composition of the instant invention wherein, upon injection into at least one parenteral site of a subject, provides at least one of the following:

(a) a therapeutic level of valdecoxib within about 10, alternatively about 5, or alternatively about 3 hours after depot administration;

(b) a therapeutic level of valdecoxib for at least about 2, alternatively for at least about 3, or alternatively for at least about 4 days;

(c) a time to reach a maximum blood serum concentration ($T_{1/2max}$) of valdecoxib that is not greater than about 20, alternatively not greater than about 10, or alternatively not greater than about 3 hours after administration.

[00024] This invention also provides a method for preparing Mg diparecoxib, the method comprising an *in situ* crystallization method.

[00025] This invention also provides a method for preparing Mg diparecoxib, the method comprising the step of precipitating diparecoxib magnesium from parecoxib free acid, for example by reacting $MgOH_2$ with solublized parecoxib free acid ("parecoxib FA").

## BRIEF DESCRIPTION OF THE DRAWING(S)

[00026] Fig 1 shows the UV absorbance spectra of the supernatants from *in-situ* crystallization of the parecoxib salts as described in Example 1.

[00027] Fig 2 shows a 600X magnification of Ca diparecoxib crystals 600X.

[00028] Fig 3 shows a 600X magnification of Mg diparecoxib crystals.

[00029] Fig 4 shows time dependant solubilization of a Mg diparecoxib, parecoxib free acid, and valdecoxib suspensions in a dissolution apparatus.

[00030] Fig 5 shows microscopy of parecoxib free acid formed in Example 4.

[00031] Fig 6 shows microscopy of Mg diparecoxib formed in Example 4.

[00032] Fig 7 shows microscopy of valdecoxib formed in Example 4.

[00033] Fig 8 shows plasma levels of valdecoxib after suspension of Example 4 were injected into dogs.

[00034] Fig 9 shows cumulative input rate of valdecoxib from Example 5.

[00035] Fig 10 shows plasma valdecoxib concentration with time following Mg diparecoxib depot administration to dogs.

[00036] Fig 10 shows theoretical plasma valdecoxib levels that are predicted to follow Mg diparecoxib depot administration to humans.

## DETAILED DESCRIPTION OF THE INVENTION

**Magnesium salt of parecoxib.**

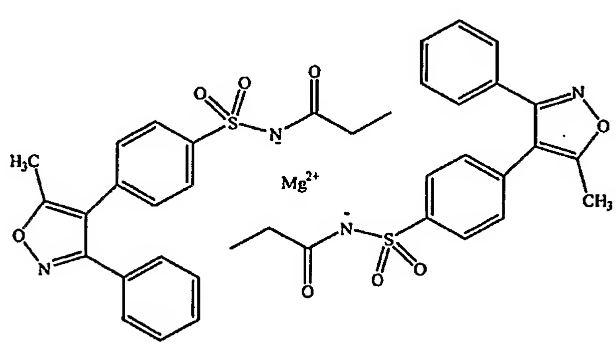
[00037] Compounds of the present invention are selective COX-2 inhibitors. The terms "cyclooxygenase-1" and "COX-1" used interchangeably herein refer to the constitutive isoform of the enzyme cyclooxygenase. The terms "cyclooxygenase-2" and "COX-2 as used interchangeably herein refer to the inducible isoform of the enzyme cyclooxygenase. The term "COX-2 selectivity" has been given numerous and varied definitions in the published literature. Selectivity has been understood to refer, alternatively, to a variety of in vitro conditions and to a variety of in vivo conditions. In vitro selectivity does not necessarily mean the same thing as in vivo selectivity. However, as used herein, the terms "cyclooxygenase-2 selective inhibitor" and "COX-2 selective inhibitor" are used interchangeably herein and for the present invention refer to a therapeutic compound that inhibits cyclooxygenase-2 more than it inhibits cyclooxygenase-1 in an in vitro recombinant enzyme assay. The

term "cyclooxygenase-2 inhibitor" or "COX-2 inhibitor" refers to any compound which inhibits the COX-2 enzyme, without regard to the extent to which it inhibits COX-1. Especially suitable as cyclooxygenase-2 selective inhibitors useful in the present invention are those compounds that have a cyclooxygenase-2 $IC_{50}$ of less than about 0.2 μM, and also have a selectivity ratio of cyclooxygenase-2 inhibition over cyclooxygenase-1 inhibition of at least 50 or alternatively, at least 100. In another embodiment, the cyclooxygenase-2 selective inhibitor compounds have a cyclooxygenase-1 $IC_{50}$ of greater than about 1 μM or alternatively, greater than 10 μM.

**[00038]** In one embodiment, the selective COX-2 inhibitory compound of the present invention is a magnesium salt of parecoxib having the structure $MgX^1X^2$, wherein $X^1$ is parecoxib anion and $X^2$ is selected from the group consisting of parecoxib anion and another pharmaceutically acceptable anion. One skilled in the art can readily recognize that pharmaceutically acceptable anions can be inorganic (e.g. such as chloride, bromide, sulfate, phosphate, and nitrate) or organic (e.g. acetate, propionate, succinate, glycolate, stearate, lactate, malate, tartrate, citrate, ascorbate, glutamate, benzoate, salicylate, methanesulfonate, and toluenesulfonate).

**[00039]** In a desired embodiment, the magnesium salt of parecoxib is substantially in the form of Formula I and referred to herein as magnesium diparecoxib (or Mg diparecoxib).

**[00040]** Formula I



**[00041]** Whereas Formula I depicts one magnesium cation in salt bridge with two parecoxib anions, the compound of the instant invention is not so limited to this

stoichiometry. Instead, the Formula I depiction and the term "magnesium diparecoxib" reflects the inventors' understanding of the molecular form. The term "substantially in the form of" Formula I is meant to embrace molecular forms wherein the parecoxib anion to magnesium caion molar ratio is about 1.5 to about 2.5.

**[00042]** In one embodiment, magnesium diparecoxib is crystalline. In a desired embodiment, magnesium salts of the present invention are non-needle-like crystals, for example cuboidal or polygonal crystals. In one embodiment of the present invention is of a form having a relatively low surface area to volume ratio (especially when compared to needle-like crystals). The term "relatively low", in this context, means a surface to volume ratio less than about 48 microns $^{-1}$, alternatively less than about 24 microns $^{-1}$, or alternatively less than about 12 microns $^{-1}$.

**[00043]** In an alternative embodiment, in absence of milling or sonnication or the like, Mg diparecoxib crystals have an average particle size, using Horiba Particle Sizer, of about 40 microns. In absence of milling or sonnication or the like, the crystals of the present invention have a $D_{90}$ (by weight) of less than about 100 microns, alternatively less than about 60 microns, alternatively about 40 microns (based upon the longest length of the crystal).

**[00044]** After 1 min sonication of an alternative embodiment, the crystals have an average particle size, using Horiba Particle Sizer, of about 20 microns. Alternatively, such crystals have a $D_{90}$ (by weight) of less than about 60 microns, alternatively less than about 40 microns, alternatively about 20 microns (based upon the longest length of the crystal).

**Synthesis of diparecoxib magnesium.**

**[00045]** Two exemplary methods are contemplated herein to prepare Mg diparecoxib.

Method I – Precipitation from parecoxib free acid

**[00046]** Parecoxib free acid is prepared as taught in U.S. Patent No. 5,932,598. Next, parecoxib free acid [FA] is suspended or dissolved in a liquid. For example, a 75 mM suspension of parecoxib FA is made in ethanol. Additionally, a magnesium salt (e.g. $Mg(OH)_2$, $MgCl_2$ or Mg) is suspended or dissolved in a second liquid. For example, a 55 mM suspension of $Mg(OH)_2$ is made in ethanol. Next, the suspension

or solution of parecoxib FA and a magnesium salt are combined. For example 3 parts of the aforementioned 75 mM parecoxib FA suspension is combined with 2 parts of the aforementioned 55 mM $Mg(OH)_2$ suspension. In one alternative, in the combined suspension or solution, the molar ratio of parecoxib anion to the magnesium cation is 2 to 1, alternatively the molar ratio is more than about one to one and less than about four to one. Next, the combination is agitated (e.g. stirred) for a period of time (e.g. for 10 minutes or more). During this agitation period, magnesium salt of parecoxib precipitates. The precipitates are collected, for example by centrifugation or by evaporating the ethanol (e.g. *in vacuo).* Optionally, the crystals are dried (e.g. at high vacuum).

Method II - *in situ* crystallization.

**[00047]** Sodium parecoxib sodium is prepared as taught in U.S. Patent No. 5,932,598. Next, sodium parecoxib is dissolved in a liquid. For example the liquid can be water, and optionally the liquid is buffered. By way of example, 15 mM Tris is adjusted to a slightly basic pH (e.g. pH 8; to avoid formation of valdecoxib) and sodium parecoxib is dissolved therein at a useful concentration (e.g., at 10 – 40 mg parecoxib free acid equivalents/ml) to form a solution. This solution is combined with a concentrated magnesium salt solution (e.g. $MgCl_2$ or Mg sulfate). Optionally, the parecoxib solution and the magnesium salt solution are combined such that the molar ratio of parecoxib anion to cation is greater than about 1, optionally greater than about 1.5 or greater than about 2. Next, the combination is agitated (e.g. stirred) for a period of time (e.g. for about one to about 30 minutes or for overnight). During this agitation period, the magnesium salt of parecoxib precipitates. After the agitation period, Mg diparecoxib precipitates are separated from the solution, for example by centrifugation or filtration.

**[00048]** Other variations preparing Mg diparecoxib are set forth below by way of working examples. A skilled artisan can understand that, based upon the disclosure herein, Ca diparecoxib, Zn diparecoxib, and K parecoxib can similarly be made. For example, K parecoxib can be made by adding KOH to parecoxib free acid by the procedure taught above.

**Diparecoxib(2)Mg compositions**

[00049] In one embodiment, a composition of the instant invention comprises a dosage form comprising Mg parecoxib and one or more pharmaceutically acceptable excipients. Based upon the disclosure herein, one of skill in the art can select one or more pharmaceutically acceptable excipients selected according to the desired: (1) route of administration, (2) plasma levels of valdecoxib, and (3) duration of therapeutic levels of circulating valdecoxib.

[00050] In one embodiment, the instant composition comprises Mg parecoxib in an amount of at least about 1% by weight of the total composition weight, alternatively at least about 10% or at least about 20% by weight.

**Orally deliverable solid article composition**

[00051] In another embodiment, a composition of the instant invention is in an oral dose unit in the form of discrete solid articles such as tablets, pills, hard or soft capsules, lozenges, sachets or pastilles; alternatively the composition can be in the form of a substantially homogeneous flowable mass, such as a particulate, powder, or granular solid or a liquid suspension, from which single dose units are measurably removable.

**Parenterally deliverable composition**

[00052] In a preferred embodiment, the composition of the instant invention comprises Mg diparecoxib in a form suitable for parenteral administration. The term "parenteral administration" herein encompasses injection and/or infusion of a composition into or through the skin of a subject, and includes, without limitation, intradermal, subcutaneous, intramuscular, intravenous, intramedullary, intra-articular, intraperitoneal, intralymphoid, intrasynovial, intraspinal, intrathecal, subdural, and intracardiac administration. Any known device useful for parenteral injection or infusion of drugs can be used to effect such administration.

[00053] Parenterally deliverable embodiments of the instant invention satisfy one or more, optionally three or more, optionally five or more, optionally seven or more, or optionally nine or more of the following criteria: sterility, low endotoxin level, defined particle size range, no "caking" during shelf life, easy redispersion with mild shaking, slow rate of settling after redispersion, homogeneity of suspension after redispersion, syringeable and injectable through narrow gauge needle, formulation

isotonicity and pH close to physiologic range, physical particle stability (e.g. no polymorphism or crystal growth), and chemical stability.

[00054] Parenterally deliverable composition of the instant invention comprise (a) Mg diparecoxib in a therapeutically effective amount; optionally (b) a parenterally acceptable buffer for adjusting and/or maintaining pH of the composition; optionally (c) an isotonicity agent; optionally (d) a suspending agent to reduce undesired settling out of Mg diparecoxib in liquid compositions; and optionally (e) a solubilizing agent.

[00055] Where it is desired to have the Mg diparecoxib in a soluble composition (e.g. for intravenous administration), a solubilizing agent can comprise, for example, at least one cyclodextrin. Cyclodextrins suitable for use in a composition of the invention can be α-cyclodextrins or β-cyclodextrins (also referred to herein as β-CD). Optionally, the cyclodextrins are β-cyclodextrins. Among these optional cyclodextrin derivatives are those wherein the $C_{2-6}$ alkylene is a $C_3$ or $C_4$ alkylene. Also among these optional cyclodextrins is sulfoalkylether β-cyclodextrin, for example sulfobutylether-β-cyclodextrin having an average substitution of about 4 to about 8 and preferably about 5 to about 7, for example about 6.4 sulfobutyl ether linkages (*i.e.* sulfobutyl ether$_{6.4}$-β–cyclodextrin).

[00056] The composition of the instant invention can comprise at least one non-aqueous solubilizing agent such as a polyethylene glycol, ethanol, dimethylacetamide (DMAC), a propylene glycol, and mixtures thereof.

[00057] Compositions of the instant invention optionally comprise a isotonicity agent, for example NaCl, sorbitol, mannitol, dextrose, polyethylene glycols ("PEGs"), phosphate buffers, methyl and propyl parabens, polyethylene glycols, carboxymethylcelluloses, alginate, polyvinyl pyrrolidones, and polysorbates.

[00058] As used herein, "isotonic" means that the osmolarity of the solution is substantially the same as the physiological osmolarity (the tonicity or osmotic pressure of the solution is similar to that of blood).

[00059] In one parenterally deliverable composition of the instant invention, the composition is in powder form. The powder form is optionally reconstitutable in a

parenterally acceptable solvent liquid, optionally an aqueous liquid, to form a solution suitable for injection.

**[00060]** The parenterally deliverable composition in powder form can be prepared by a process comprising a step of removing water from an aqueous solution (by, for example, lyophilization) comprising Mg diparecoxib and optionally one or more buffers, a isotonicity agent, and a suspending agent to form a readily reconstitutable powder.

**[00061]** In one embodiment, the invention is an article of manufacture comprising a sealed vial having contained therewithin a sterile, parenterally deliverable composition of the instant invention in powder form. One skilled in the art can recognize that such an article of manufacture can optionally contain a useful volume of a solvent (e.g. water) sequestered from the powder form in a compartment that allows mixing of the water and the powder form before use without opening the sealed vial.

**[00062]** In another embodiment, the invention is an injectable solution prepared by reconstitution of the composition.

**[00063]** In another embodiment, the invention is an article of manufacture comprising a sealed vial having contained therewithin a unit dosage amount of the composition in a sterile condition.

## Depot Composition

**[00064]** In one embodiment, the parenterally deliverably composition of the instant invention is suitable for depot administration. Such a depot administration preferably delivers a therapeutically effective dose for a sustained period of time, for example at least about two days, optionally at least about three days, optionally at least about four days, or optionally at least about five days.

**[00065]** As used herein, a "depot" is a pharmaceutical composition containing a therapeutically active agent that is suitable for administration by implantation or injection into a local site that results in a gradual release (for example, release over a few hours or a few days) of the active agent into circulation. Release of the active

agent is modulated by the nature of the site injected or implanted, the solubility of the active agent, and the precise composition of the depot.

[00066] As used herein, "depot administration" means the administration by implantation or injection, for example, subcutaneous, intramuscular, intradermal, and intra-articular administration. Thus, a depot administration is to be contrasted with, for example, an intra venous injection that results in rapid systemic delivery of the active agent (for example, within minutes of injection).

[00067] The depot compositions of the instant convention can contain Mg diparecoxib and a means for stabilizing and/or controlling solubilization rate of Mg diparecoxib. Such stabilizing and/or controlling means can be selected from suitable polymeric or hydrophobic materials or ion-exchange resins. By way of example, an emulsion can be produced from Mg diparecoxib using an acceptable oil to stabilize or control release of Mg diparecoxib.

[00068] Pharmaceutical compositions of the instant invention are characterized by at least one feature selected from the group consisting of steady extended release, useful release rate, minimal pain on injection, no local toxicity due to depot, a duration of action correlated with dose, and a correlation between *in vitro* and *in vivo* release.

[00069] Depots of the instant invention contain Mg diparecoxib at a concentration that is useful for parenteral administration and that results in a therapeutic level of valdecoxib. Such a useful concentration is about 40 to 500 mg/ml, for example about 80 mg/ml to about 280 mg/ml.

[00070] Another embodiment of the present invention is a method of administering Mg diparecoxib in depot formulation Such a method delivers an amount of Mg diparecoxib in an amount of about 40 mg to about 500 mg, optionally 60 mg to about 400 mg or optionally about 80 mg to about 280 mg.

[00071] In another embodiment, the depot composition of the instant invention contains a second therapeutically active agent. In one embodiment, the second active agent is an analgesic, an anti-pyretic, and/or an anti-inflammatory compound. In a particular embodiment, the second active agent is selective COX-2 inhibitor; optionally the selective COX-2 inhibitor is a valdecoxib pro-drug or valdecoxib. In a

particular embodiment, the second active agent delivers a therapeutic level of valdecoxib more rapidly than does Mg diparecoxib in the same embodiment. Optionally, such a composition comprises Mg diparecoxib and a second active agent in an amount such that, when administered as a depot, therapeutic levels of circulating valdecoxib attain the predicted therapeutic need over a period of two or more days. Examples of selective COX-2 inhibitors useful as the second active agent are valdecoxib, celecoxib, rofecoxib, etoricoxib, lumiracoxib, and parecoxib salts of the instant invention.

**[00072]** As disclosed herein, physicochemical properties of compounds of the present invention (e.g. Mg diparecoxib, Ca diparecoxib, Zn diparecoxib, K parecoxib, and valdecoxib) contribute, in part, to a dosage form with different pharmacokinetic properties. Such pharmacokinetic properties include, by way of example, dissolution rate, bioabsorption rate, time to reach maximum concentration ($T_{max}$), the duration of time that therapeutic (or other) levels are sustained; the termnal half-life ($T_{1/2}$); and maximum concentration ($C_{max}$).

**[00073]** Based upon such properties as disclosed herein, a skilled artisan is able to combine compounds of the present invention in absolute and relative amounts such that, when formulated and administered as a depot, any desired circulating levels of valdecoxib can be achieved, even if such desired levels predictably change with time following administration.

**[00074]** By way of example, in a certain circumstance it is desired to rapidly achieve a first therapeutic level, for example 75 ng valdecoxib/ml plasma. It can be desirable to sustain such first therapeutic level for a certain first period of time, for example two day. Moreover, in the same such circumstance after the first period of time, it can be desired to achieve a second therapeutic level for a second period of time, for example 25 ng valdecoxib/ml plasma for four days. Moreover, in the same such circumstance after the second period of time, it can be desired to achieve a third valdecoxib level for a third period of time. Such third level can be a changing level (for example 25 ng valdecoxib/ml plasma) decreasing to zero ng valdecoxib/ml plasma over the course of the third period of time (for example, two days).

**[00075]** Examples of situations where the therapeutic need could change with time are conditions wherein there is a rapid onset of pain and conditions of acute pain,

where the physiologic healing process is expected to reduce the therapeutic need with time. Specific instance include, by way of example, oral surgery, surgical removal of a tissue (e.g. biopsy or appendectomy), vaccination, cosmetic surgery, etc.

**[00076]** Examples of such embodiments are a dosage form comprising (1) Mg diparecoxib and Na parecoxib (2) Mg diparecoxib and Ca diparecoxib; (3) Mg diparecoxib and Zn diparecoxib; (4) Mg diparecoxib and K parecoxib; and (5) Mg diparecoxib and valdecoxib.

**[00077]** Compositions of the invention are useful in subjects for treatment and prevention of a very wide range of disorders mediated by COX-2, including but not restricted to disorders characterized by inflammation, pain and/or fever. Such composition possess the additional benefit of having significantly less harmful side effects than compositions of conventional NSAIDs that lack selectivity for COX-2 over COX-1. In particular, compositions of the invention have reduced potential for gastrointestinal toxicity and gastrointestinal irritation, including upper gastrointestinal ulceration and bleeding, by comparison with compositions of conventional NSAIDs. Thus compositions of the invention are particularly useful as an alternative to conventional NSAIDs where such NSAIDs are contraindicated, for example in subjects with peptic ulcers, gastritis, regional enteritis, ulcerative colitis, diverticulitis or with a recurrent history of gastrointestinal lesions; gastrointestinal bleeding, coagulation disorders including anemia such as hypoprothrombinemia, hemophilia or other bleeding problems; kidney disease; or in subjectss prior to surgery or subjects taking anticoagulants.

**[00078]** Compositions of the instant invention are useful in treating a condition or disorder where treatment with a COX-2 inhibitory drug is indicated. More preferred uses include treatment for an acute condition (e.g. a condition where treatment is need for a period of several days to several weeks).

**[00079]** Compositions of the instant invention are useful in treatment of pain, including but not limited to perioperative pain, postoperative pain, post-oral surgery pain, post-general surgery pain, post-orthopedic surgery pain, dental pain, muscular pain, and pain resulting from cancer.

[00080] It is now disclosed that a single administration of a depot composition of the instant invention within one week prior to surgery reduces perioperative pain (i.e. pain associated with the surgical procedure itself and the more intense and/or acute pain following the surgery) and reduces post operative pain (i.e. pain following the more intense and/or acute pain phase). It should be understood that the distinction between late preoperative pain phase and early post-operative pain phase is sometime unclear or non-existent. Examples of such a useful pre-operative injection regimen is an injection minutes prior to surgery, optionally within 24 hours before surgery, optionally within 48 hours before surgery, or optionally within one week before surgery.

[00081] It has further been the surprising discovery that a single administration of a depot composition of the instant invention within the aforementioned useful pre-operative injection regimen reduces the need for administration of an opiate for analgesia.

[00082] Compositions of the instant invention are useful for relief of pain, fever and inflammation in a variety of conditions including rheumatic fever, influenza and other viral infections including common cold, low back and neck pain, dysmenorrhea, headache, toothache, sprains and strains, myositis, neuralgia, synovitis, arthritis, including rheumatoid arthritis, degenerative joint diseases (osteoarthritis), gout and ankylosing spondylitis, bursitis, burns, radiation damage, and trauma following surgical and dental procedures.

[00083] Contemplated compositions are useful to treat a variety of arthritic disorders, including but not limited to rheumatoid arthritis, spondyloarthropathies, gouty arthritis, osteoarthritis, systemic lupus erythematosus and juvenile arthritis.

[00084] Such compositions are useful for treating and preventing inflammation-related cardiovascular disorders, including vascular diseases, coronary artery disease, aneurysm, vascular rejection, arteriosclerosis, atherosclerosis including cardiac transplant atherosclerosis, myocardial infarction, embolism, stroke, thrombosis including venous thrombosis, angina including unstable angina, coronary plaque inflammation, bacterial-induced inflammation including Chlamydia-induced inflammation, viral induced inflammation, and inflammation associated with surgical procedures such as vascular grafting including coronary artery bypass surgery,

revascularization procedures including angioplasty, stent placement, endarterectomy, or other invasive procedures involving arteries, veins and capillaries.

**[00085]** Such compositions of the instant invention are useful in prevention and treatment of benign and malignant tumors and neoplasia including cancer, such as colorectal cancer, brain cancer, bone cancer, epithelial cell-derived neoplasia (epithelial carcinoma) such as basal cell carcinoma, adenocarcinoma, gastrointestinal cancer such as lip cancer, mouth cancer, esophageal cancer, small bowel cancer, stomach cancer, colon cancer, liver cancer, bladder cancer, pancreas cancer, ovary cancer, cervical cancer, lung cancer, breast cancer, skin cancer such as squamous cell and basal cell cancers, prostate cancer, renal cell carcinoma, and other known cancers that effect epithelial cells throughout the body. Neoplasias for which compositions of the invention are contemplated to be particularly useful are gastrointestinal cancer, Barrett's esophagus, liver cancer, bladder cancer, pancreatic cancer, ovarian cancer, prostate cancer, cervical cancer, lung cancer, breast cancer and skin cancer. Such compositions can also be used to treat fibrosis that occurs with radiation therapy. Such compositions can be used to treat subjects having adenomatous polyps, including those with familial adenomatous polyposis (FAP). Additionally, such compositions can be used to prevent polyps from forming in subjects at risk of FAP.

**[00086]** Subjects undergoing treatment with a composition of the invention can be routinely monitored by any of the methods well known in the art to determine effectiveness of therapy. Continuous analysis of data from such monitoring permits modification of the treatment regimen during therapy so that optimally effective doses are administered at any point in time, and so that the duration of treatment can be determined. In this way, the treatment regimen and dosing schedule can be rationally modified over the course of therapy so that the lowest amount of the composition exhibiting satisfactory effectiveness is administered, and so that administration is continued only for so long as is necessary to successfully treat the condition or disorder.

**[00087]** Parecoxib salts of the instant invention (e.g. Mg parecoxib(2), Zn parecoxib(2), Ca parecoxib(2), and K parecoxib when administered parenterally to a human subject, is rapidly and completely converted to valdecoxib. Therefore, a therapeutically effective dose of parecoxibs of the instant invention is one that

delivers a therapeutically effective circulating dose of valdecoxib. By was of example, thereapeutic levels typically are at least about 20 ng/ml plasma, for example about 25 to about 75 ng/ml.

[00088] Therapeutic methods of the instant invention further include combination therapies of parecoxib or a composition of the invention with one or more drugs selected from opioids and other analgesics, including narcotic analgesics, Mu receptor antagonists, Kappa receptor antagonists, non-narcotic (i.e. non-addictive) analgesics, monoamine uptake inhibitors, adenosine regulating agents, cannabinoid derivatives, Substance P antagonists, neurokinin-1 receptor antagonists and sodium channel blockers, among others. Preferred combination therapies comprise use of a composition of the invention with one or more compounds selected from aceclofenac, acemetacin, *e*-acetamidocaproic acid, acetaminophen, acetaminosalol, acetanilide, acetylsalicylic acid (aspirin), *S*-adenosylmethionine, alclofenac, alfentanil, allylprodine, alminoprofen, aloxiprin, alphaprodine, aluminum bis(acetylsalicylate), amfenac, aminochlorthenoxazin, 3-amino-4-hydroxybutyric acid, 2-amino-4-picoline, aminopropylon, aminopyrine, amixetrine, ammonium salicylate, ampiroxicam, amtolmetin guacil, anileridine, antipyrine, antipyrine salicylate, antrafenine, apazone, bendazac, benorylate, benoxaprofen, benzpiperylon, benzydamine, benzylmorphine, bermoprofen, bezitramide, α-bisabolol, bromfenac, *p*-bromoacetanilide, 5-bromosalicylic acid acetate, bromosaligenin, bucetin, bucloxic acid, bucolome, bufexamac, bumadizon, buprenorphine, butacetin, butibufen, butophanol, calcium acetylsalicylate, carbamazepine, carbiphene, carprofen, carsalam, chlorobutanol, chlorthenoxazin, choline salicylate, cinchophen, cinmetacin, ciramadol, clidanac, clometacin, clonitazene, clonixin, clopirac, clove, codeine, codeine methyl bromide, codeine phosphate, codeine sulfate, cropropamide, crotethamide, desomorphine, dexoxadrol, dextromoramide, dezocine, diampromide, diclofenac sodium, difenamizole, difenpiramide, diflunisal, dihydrocodeine, dihydrocodeinone enol acetate, dihydromorphine, dihydroxyaluminum acetylsalicylate, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, diprocetyl, dipyrone, ditazol, droxicam, emorfazone, enfenamic acid, epirizole, eptazocine, etersalate, ethenzamide, ethoheptazine, ethoxazene, ethylmethylthiambutene, ethylmorphine, etodolac, etofenamate, etonitazene, eugenol, felbinac, fenbufen, fenclozic acid, fendosal, fenoprofen, fentanyl, fentiazac, fepradinol, feprazone,

floctafenine, flufenamic acid, flunoxaprofen, fluoresone, flupirtine, fluproquazone, flurbiprofen, fosfosal, gentisic acid, glafenine, glucametacin, glycol salicylate, guaiazulene, hydrocodone, hydromorphone, hydroxypethidine, ibufenac, ibuprofen, ibuproxam, imidazole salicylate, indomethacin, indoprofen, isofezolac, isoladol, isomethadone, isonixin, isoxepac, isoxicam, ketobemidone, ketoprofen, ketorolac, *p*-lactophenetide, lefetamine, levorphanol, lofentanil, lonazolac, lornoxicam, loxoprofen, lysine acetylsalicylate, magnesium acetylsalicylate, meclofenamic acid, mefenamic acid, meperidine, meptazinol, mesalamine, metazocine, methadone hydrochloride, methotrimeprazine, metiazinic acid, metofoline, metopon, mofebutazone, mofezolac, morazone, morphine, morphine hydrochloride, morphine sulfate, morpholine salicylate, myrophine, nabumetone, nalbuphine, 1-naphthyl salicylate, naproxen, narceine, nefopam, nicomorphine, nifenazone, niflumic acid, nimesulide, 5'-nitro-2'-propoxyacetanilide, norlevorphanol, normethadone, normorphine, norpipanone, olsalazine, opium, oxaceprol, oxametacine, oxaprozin, oxycodone, oxymorphone, oxyphenbutazone, papaveretum, paranyline, parsalmide, pentazocine, perisoxal, phenacetin, phenadoxone, phenazocine, phenazopyridine hydrochloride, phenocoll, phenoperidine, phenopyrazone, phenyl acetylsalicylate, phenylbutazone, phenyl salicylate, phenyramidol, piketoprofen, piminodine, pipebuzone, piperylone, piprofen, pirazolac, piritramide, piroxicam, pranoprofen, proglumetacin, proheptazine, promedol, propacetamol, propiram, propoxyphene, propyphenazone, proquazone, protizinic acid, ramifenazone, remifentanil, rimazolium metilsulfate, salacetamide, salicin, salicylamide, salicylamide *o*-acetic acid, salicylsulfuric acid, salsalte, salverine, simetride, sodium salicylate, sufentanil, sulfasalazine, sulindac, superoxide dismutase, suprofen, suxibuzone, talniflumate, tenidap, tenoxicam, terofenamate, tetrandrine, thiazolinobutazone, tiaprofenic acid, tiaramide, tilidine, tinoridine, tolfenamic acid, tolmetin, tramadol, tropesin, viminol, xenbucin, ximoprofen, zaltoprofen and zomepirac (see The Merck Index, 12th Edition, Therapeutic Category and Biological Activity Index, ed. S. Budavari (1996), pp. Ther-2 to Ther-3 and Ther-12 (Analgesic (Dental), Analgesic (Narcotic), Analgesic (Non-narcotic), Anti-inflammatory (Non-steroidal)).

**[00089]** Therapeutic methods of the instant invention further include combination therapies of the Mg diparecoxib, valdecoxib, or other parecoxib salts of the instant invention with one or more drugs selected from antineoplastic agents (e.g.

antineoplastic topoisomerase II inhibitors, antineoplastic antimicrotubule agents, antineoplastic alkylating agents, antineoplastic antimetabolites, and antineoplastic topoisomerase I inhibitors). Antineoplastic topoisomerase II inhibitors can, by way of example, be anthracycline compounds (e.g. doxorubicin, daunomycin, methoxy-morpholino-doxorubicin, epirubicin idarubicin and nemorubicin); anthraquinone compounds (e.g. mitoxantrone and losoxantrone); and podophillotoxine compounds (e.g. etoposide and teniposide). Antimicrotubule agents can, by way of example, be taxane compounds (e.g. paclitaxel and docetaxel) and vinca alkaloids (e.g. vinblastine and vinorelbine). Alkylating agents can, by way of example, be cyclophosphamide, ifosfamide, chlorambucil, and melphalan. Antineoplastic antimetabolite agents can, by way of example, be 5-fluorouracil, capecitabine, gemcitabine, methotrexate and edatrexate. Antineoplastic topoisomerase I inhibitors can, by way of example, be topotecans, irinotecans, and 9-nitrocamptothecin.

**[00090]** As used herein, the term "subjects", as objects of treatment with compositions of the instant invention, means animals. Preferably such animals are humans or companion animals, exotic animals, farm animals, and the like, particularly mammals. Other preferred animals are horses, dogs and cats with a COX-2 mediated disorder.

**[00091]** As used herein, the term "*in vivo* administration" means administration to a subject by oral or parenteral route.

**[00092]** The instant invention is further directed to a therapeutic method of treating a condition or disorder where treatment with a COX-2 inhibitory drug is indicated, the method comprising parenteral administration of a composition of the invention to a subject in need thereof. The dosage regimen to prevent, give relief from, or ameliorate the condition or disorder is determined in accordance with a variety of factors. These include the type, age, weight, sex, diet and medical condition of the subject and the nature and severity of the disorder. Thus, the dosage regimen actually employed can vary widely.

## Working Examples

**Example 1: Preparation of Mg diparecoxib, Zn diparecoxib, Ca diparecoxib, and K parecoxib.**

**[00093]** Mg diparecoxib, Zn diparecoxib, Ca diparecoxib, and K parecoxib were prepared using *in-situ* crystallization. Briefly, solutions of Na parecoxib were prepared in water for injection (WFI) at 10 mg/ml. Salt solutions were prepared in WFI using potassium chloride, calcium chloride, magnesium chloride, or zinc chloride. Stoichiometric excess of the salt solutions were added individually to Na parecoxib solutions, and WFI was added to a control solution of Na parecoxib. After 24 hours, precipitate was visually observed in the vials to which calcium chloride, magnesium chloride, and zinc chloride were added. There was no precipitate in the vials to which either potassium chloride or water was added.

<u>Solubility Estimates of Mg diparecoxib, Zn diparecoxib, Ca diparecoxib, and K parecoxib.</u>

**[00094]** The supernatant from each vial from Working Example 1 was sampled and analyzed by UV absorbance after appropriate dilution to detect the concentration of parecoxib in solution. The solutions from the vials containing calcium, magnesium or zinc ions showed reduction in the concentration of parecoxib, indicating that the precipitates observed were those of parecoxib salts formed with the respective counterions. Thus, the amount of parecoxib in the supernatant was indirectly proportional to the water solubility of the parecoxib salt. There was no loss of parecoxib concentration in the vials where no precipitate was observed (i.e., where potassium chloride or water was added).

**[00095]** The UV absorbance spectra (Figure 1) indicated that the lowest levels of parecoxib in the supernatants were in the vials where calcium chloride or magnesium chloride were added. However, most of the parecoxib remained in solution after addition of zinc chloride, indicating that Zn diparecoxib has greater aqueous solubility as compared to the calcium or magnesium salts of parecoxib.

**[00096]** From the UV absorbance data shown in Figure 1, the relative solubilities of the salts tested were estimated to be in the following descending order (P = parecoxib): Na P ~ K P > Zn $P_2$ > Ca $P_2$ > Mg $P_2$.

**Example 2: Preparation of Mg diparecoxib and Ca diparecoxib.**

**[00097]** Since Ca diparecoxib and Mg diparecoxib exhibited the lowest solubilities of the parecoxib salts examined in Example 1, these two salt forms of parecoxib were selected for further investigation.

**[00098]** A series of compositions of calcium and magnesium salts of parecoxib were prepared by *in-situ* crystallization, starting from solutions of Na parecoxib. A slightly basic pH was selected for *in-situ* crystallization in order to avoid formation of parecoxib free acid, and to obtain compositions with near physiologic pH.

**[00099]** Sodium phosphate was tested for compatibility with the $CaCl_2$ and $MgCl_2$ reagents. However, under the conditions tested, in the absence of parecoxib, poorly soluble salts of calcium phosphate and magnesium phosphate, respectively, were formed. However, when the cationic buffer Tris was tested, no precipitate formed in the absence of parecoxib. This was believed to be due, in part, to the fact that the cationic buffer cannot form ionic salts with calcium or magnesium cations. Therefore, Tris was selected as the buffer reagent for the next experiment.

**[000100]** Ca diparecoxib and Mg diparecoxib compositions were prepared *by in situ* crystallization from parecoxib Sodium at approx 40 mg/ml in 15 mM Tris buffer (approx pH 8). Four stoichiometries of calcium and magnesium counterions were tested. Calculated volumes of 1 molar $CaCl_2$ and $MgCl_2$ salt solutions were added to buffered solutions of Na parecoxib to provide 0.5, 1, 2, and 4 molar equivalents of calcium and magnesium counterions relative to parecoxib, as per Table I. Control compositions were also prepared wherein the salt solutions were added to Tris buffer with no parecoxib present, or where water was added to Na parecoxib solution instead of salt. Visible precipitation was observed in each case soon after addition of the salt solutions to Na parecoxib solutions, and no precipitation was observed for the control compositions. The compositions were allowed to stir overnight before further analysis.

**[000101]** After overnight stirring, visual observations were made. All the Ca diparecoxib and Mg diparecoxib compositions were white aqueous suspensions. Some turbidity also developed in the Na parecoxib control composition after overnight stirring. Without limiting the scope of the invention, this turbidity was believed to result from the fact that Na parecoxib is known to form supersaturated solutions, and

its solubility is highly dependent on ionic and pH conditions. Aliquots of all the compositions were obtained and centrifuged to suspend any particles. The clear supernatants were analyzed for pH and UV absorbance (Table II). Additional aliquots of the suspensions were observed by optical microscopy under polarized light. Representative micrographs are shown in Figures 2 and 3.

**Table I. Composition Descriptions**

| Vial / Sample Codes | Stoichiometry parecoxib / $Ca^{2+}$ or $Mg^{2+}$ | Divalent Cation Added |
|---|---|---|
| PC | 1 : 0 | - |
| Ca 0.5 | 1 : 0.5 | $Ca^{2+}$ |
| Ca 1 | 1 : 1 | $Ca^{2+}$ |
| Ca 2 | 1 : 2 | $Ca^{2+}$ |
| Ca 4 | 1 : 4 | $Ca^{2+}$ |
| Ca 0.4C | 0 : 4 | $Ca^{2+}$ |
| Mg 0.5 | 1 : 0.5 | $Mg^{2+}$ |
| Mg 1 | 1 : 1 | $Mg^{2+}$ |
| Mg2 | 1 : 2 | $Mg^{2+}$ |
| Mg 4 | 1 : 4 | $Mg^{2+}$ |
| Mg 0.4 | 0 : 4 | $Mg^{2+}$ |

**Table II. Composition Observations (Visual, pH, UV Absorbance)**

| Vial / Sample Codes | Visual Appearance | Observed pH | Absorbance at 245 nm (1850x dilution) | Absorbance at 245 nm (100x dilution) |
|---|---|---|---|---|
| PC | Turbid Liquid | 8.2 | 1.010* | Not analyzed |
| Ca 0.5 | White Suspension | 8.0 | 0.508 | Not analyzed |
| Ca 1 | White Suspension | 7.9 | 0.085 | 1.541 |
| Ca 2 | White Suspension | 7.8 | 0.033 | 0.612 |
| Ca 4 | White Suspension | 7.7 | 0.023 | 0.434 |
| Ca 0.4 | Clear Solution | 7.7 | 0.001 | 0.001 |
| Mg 0.5 | White Suspension | 8.0 | 0.493 | Not analyzed |
| Mg 1 | White Suspension | 7.9 | 0.027 | 0.507 |
| Mg 2 | White Suspension | 7.9 | 0.012 | 0.223 |
| Mg 4 | White Suspension | 7.8 | 0.007 | 0.108 |
| Mg 0.4 | Clear Solution | 7.8 | 0.001 | 0.000 |

**[000102]** *Note: For comparison with absorbance of parecoxib control "PC", absorbance of freshly prepared Na parecoxib composition (without any turbidity) was 1.019.

**[000103]** The UV absorbance results in Table II demonstrated that at every stoichiometry tested, greater amounts of parecoxib salt precipitated out due to addition of magnesium cations as compared to addition of calcium cations. For example, in the case of Ca diparecoxib 1:1 composition, about 8.5% of the starting parecoxib remained in aqueous solution. In comparison, the corresponding percentage for the Mg diparecoxib 1:1 composition was 2.7% (about 1 mg/ml), suggesting that about 97% of the parecoxib in this composition was now present as suspended particles. These observations confirmed the initial result which suggested that Mg diparecoxib has lower solubility compared to the calcium salt.

**[000104]** Optical microscopy of the suspension compositions showed that needle like crystals were formed for Ca diparecoxib (Fig 2), whereas Mg diparecoxib crystals exhibited cuboidal / polygonal morphology (Fig 3). The latter crystal morphology is relatively more desirable for several reasons: reduced surface area for dissolution (leading to slow release), easier syringeability, and reduced likelihood of pain at injection site.

**Example 3: In vitro solubility of Mg diparecoxib.**

**[000105]** In vitro solubility of dry powder of Mg diparecoxib was determined in various dissolution media and compared to solubility of parecoxib free acid and valdecoxib. As shown in Table III, solubility of dry powder of Mg diparecoxib in acidic media was similar to parecoxib free acid, solubility of Mg diparecoxib in phosphate buffer at near-physiologic pH was substantially higher than that of parecoxib free base.

__Table III__

| | Valdecoxib | parecoxib free acid | Mg diparecoxib |
|---|---|---|---|
| Dissolution Media | mg/L media | mg/L media | mg/L media |
| 0.1N HCl | 97 | 39 | 39 |
| 0.01N HCl | 197 | 59 | 72 |
| 0.01N HCl + 0.1% SDS | 243 | 292 | 380 |

| | | | |
|---|---|---|---|
| 0.5% SDS | 1,180 | 940 | 19,200 |
| 1% Bile salts | 297 | 5,170 | 19,600 |
| pH 6.8 phosphate buffer | 90.7 | 6,150 | 11,500 |
| pH 7.4 phosphate buffer | 89.5 | 14,500 | 19,400 |

[000106] The time dependant solubilization of a Mg diparecoxib suspension in a pH 6.8 phosphate buffer was examined by adding 1.5 ml of a of 40 mg/ml suspension to 98.5 mL of buffer in a dissolution apparatus. At times indicated in Table IV, suspension samples were analyzed for soluble drug content. As shown in Table II and Figure 4, Mg diparecoxib surprisingly revealed a very rapid solubilization, a plateau for about 20 hours, and then a gradual increase in solubilization with time. This gradual solubilization phase roughly paralleled parecoxib free acid ("FA"), but in an amount substantially higher than the free acid.

**Table IV**

| | Valdecoxib | parecoxib FA | Mg diparecoxib |
|---|---|---|---|
| Time (hour) | mg/ml | mg/ml | mg/ml |
| 0.033 | 0.008 | 0.033 | 0.285 |
| 0.083 | 0.012 | 0.057 | 0.283 |
| 0.250 | 0.015 | 0.089 | 0.290 |
| 0.500 | 0.017 | 0.116 | 0.293 |
| 1.000 | 0.018 | 0.135 | 0.299 |
| 2.000 | 0.018 | 0.164 | 0.296 |
| 17.000 | 0.021 | 0.210 | 0.296 |
| 24.000 | 0.014 | 0.232 | 0.345 |
| 89.000 | 0.025 | 0.309 | 0.397 |

**Example 4: Composition of Mg diparecoxib, parecoxib free acid, and valdecoxib.**

[000107] Mg diparecoxib, parecoxib free acid, and valdecoxib were formulated into pharmaceutically acceptable suspensions set forth in Table V. The starting material for Mg diparecoxib composition was prepared by *in-situ* crystallization by controlled addition of $MgCl_2$ (at a slight excess) to a sterile filtered solution of Na parecoxib.

[000108] The starting material for valdecoxib was prepared by *in situ* crystallization using controlled addition of a valdecoxib/PEG 400 solution to a sterile filtered aqueous buffer (set forth below).

[000109] The starting material for parecoxib free acid was prepared by *in-situ* crystallization by controlled addition of hydrochloric acid to a sterile filtered solution of Na parecoxib.

Table V

| Valdecoxib | parecoxib free acid | Mg diparecoxib |
|---|---|---|
| 34 mg/ml | 40 mg/ml | 42 mg/ml |
| sodium phosphate 10 mM, pH 7.5 | sodiuum acetate 10 mM pH 5 | Tris HCl 10 mM, pH 7.5 |
| Mannitol 5% w/v | Mannitol 5% w/v | Mannitol 5% w/v |
| PEG 400 20% w/v | PEG 3350 5% w/v | |
| | | $Mg_2Cl$ 5 mM |
| | Sodium Chloride ~ 100 mM | Sodium Chloride ~ 100 mM |
| | Polysorbate 80 – 0.05% v/v | |

[000110] The parecoxib free acid, Mg diparecoxib, and valdecoxib crystals formed in the compositions above were analyzed by microscopy and shown in Figures 5, 6, and 7 (respectively).

[000111] Parecoxib free acids crystals were cuboidal or polygonal. Average particle size (using Horiba Particle Sizer) was about 28 microns. After 1 min sonication, average particle size was about 16 microns .

[000112] Mg diparecoxib crystals were cuboidal or polygonal. Average particle size (using Horiba Particle Sizer) was about 40 microns. After 1 min sonication, average particle size was about 20 microns. Thus, the crystals of Mg diparecoxib have the surprising result of having properties especially favorable for depot formulation, that is reduced surface area for dissolution (leading to slow release), easier syringeability, and less pain at injection site.

[000113] Valdecoxcib crystals were cuboidal or polyagonal. Average particle size (using Horiba Particle Sizer) was about 75 microns. After 1 min sonication, average particle size was about 18 microns.

**Example 5: Screening of Mg diparecoxib Compositions**

[000114] Ten Mg diparecoxib suspension compositions were prepared at a 20 ml volume and at 40 mg/ml concentration to evaluate effect of different excipients (1). The compositions were prepared by in-situ crystallization, starting from solutions of Na parecoxib in Tris buffer. Two different reagents – Magnesium Chloride and Magnesium Sulfate were evaluated as source of magnesium ions for the in-situ salt formation. Five compositions were prepared with each of these two reagents, and with various excipients.

Composition Descriptions

[000115] McP F#1: Mg diparecoxib in 10 mM Tris buffer, prepared from Na parecoxib and magnesium chloride.

[000116] MsP#1: Mg diparecoxib in 10 mM Tris buffer, prepared from Na Parecoxib and magnesium sulfate.

[000117] McP F#2: Mg diparecoxib in 10 mM Tris buffer and 0.9% sodium chloride, prepared from Na parecoxib and magnesium chloride.

[000118] MsP#2: Mg diparecoxib in 10 mM Tris buffer and 0.9% sodium chloride, prepared from Na parecoxib and magnesium sulfate.

[000119] McP F#3: Mg diparecoxib in 10 mM Tris buffer, 0.9% sodium chloride and 0.05% Polysorbate 80, prepared from Na parecoxib and magnesium chloride.

[000120] MsP#3: Parecoxib(2)Mg in 10 mM Tris buffer, 0.9% sodium chloride and 0.05% Polysorbate 80, prepared from Na parecoxib and magnesium sulfate.

[000121] McP F#4: Mg diparecoxib in 10 mM Tris buffer and 5% mannitol, prepared from Na Parecoxib and magnesium chloride.

[000122] MsP#4: Mg diparecoxib in 10 mM Tris buffer and 5% mannitol, prepared from Na parecoxib and magnesium sulfate.

[000123] McP F#5: Mg diparecoxib in 10 mM Tris buffer, 5% mannitol and 3% PEG 3350, prepared from Na parecoxib and magnesium chloride.

[000124] MsP#5: Mg diparecoxib in 10 mM Tris buffer and 5% mannitol and 3% PEG 3350, prepared from Na parecoxib and magnesium sulfate.

[000125] All the compositions were successfully prepared, and white suspensions were obtained. During preparation, nucleation of the compositions was necessary with a few microliters of a Mg diparecoxib composition prepared separately at a smaller 5 ml scale (no nucleation was necessary at the smaller scale).

[000126] The suspension compositions were analyzed by visual appearance, pH, UV absorbance in supernatant, redispersability, syringeability, sedimentation volume, dose transfer accuracy and optical microscopy. A summary of the results is provided in Table V-I. It was noted that slightly more Mg diparecoxib remained in solution for the compositions prepared with magnesium sulfate. Overall, among the ten compositions, the composition "McP F#4" prepared by adding magnesium chloride to Na parecoxib in Tris buffer and 5% Mannitol was selected as the composition to pursue further.

**Table V-I. Screening and Selection of Mg diparecoxib Compositions**

**Compositions prepared with Magnesium Chloride**

| Composition and Reagent Description | McP F#1 In Tris buffer 10mM | McP F#2 Tris + NaCl 0.9% | McP F#3 Tris + NaCl 0.9% + PS80 0.1% | McP F#4 Tris + Mannitol 5% | McP F#5 Tris + Mannitol PEG3350 3% |
|---|---|---|---|---|---|
| Equivalent Stoichiometry / Molar Stoichiometry P:Mg | **1 : 1.1**<br>**1 : 0.55** | **1 : 1.1**<br>**1 : 0.55** | **1 : 1.1**<br>**1 : 0.55** | **1 : 1.1**<br>**1 : 0.55** | **1 : 1.1**<br>**1 : 0.55** |
| PH | **7.6** | **7.6** | **7.6** | **7.6** | **7.6** |
| Redispersability at ~ 48 h (# inversions to resuspend) | **15, 12** | **12, 14** | **18, 21** | **11, 12** | **14, 15** |
| Sedimentation Volume at ~48 h (of 5 ml suspension) | **~ 0.9 ml** | **~ 0.9 ml** | **~ 0.6 ml** | **~ 0.9 ml** | **~ 1.0 ml** |
| Sedimentation Volume at ~3 min (of 5 ml suspension) | **~ 2.0 ml** | **~ 2.0 ml** | **~ 4.7 ml** | **~ 1.7 ml** | **~ 2.0 ml** |
| Syringeability at ~ 48 h - 27 Gauge needle, 1 cc. Syringe | **Pass** | **Pass** | **Pass** | **Pass** | **Pass** |
| $Absorbance_{245\,nm}$ > 48 h in supernatant (100x dilution) | **0.364** | **0.356** | **0.422** | **0.322** | **0.458** |
| Dose Accuracy with 27 gauge needle, 1cc syringe | **81.9%** | **86.8%** | **92.5%** | **98.9%** | **107.8%** |
| Microscopy | **~ 2–10μ** | **~ 2–10μ** | **~ 2–10μ** | **~ 2–10μ** | **~ 2–10μ** |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | |

**Compositions prepared with Magnesium Sulfate**

| Composition and Reagent Description | MsP#1 In Tris buffer 10mM | MsP#2 Tris + NaCl 0.9% | MsP#3 Tris + NaCl 0.9% + PS80 0.1% | MsP#4 Tris + Mannitol 5% | MsP#5 Tris + Mannitol PEG3350 3% |
|---|---|---|---|---|---|
| Equivalent Stoichiometry / Molar Stoichiometry P:Mg | **1 : 1.1** **1 : 0.55** | **1 : 1.1** **1 : 0.55** | **1 : 1.1** **1 : 0.55** | **1 : 1.1** **1 : 0.55** | **1 : 1.1** **1 : 0.55** |
| pH | **7.7** | **7.7** | **7.7** | **7.7** | **7.7** |
| Redispersability @ ~ 48 h (# inversions to resuspend) | **13, 12** | **11, 10** | **13, 16** | **13, 12** | **12, 13** |
| Sedimentation Volume at ~48 h (of 5 ml suspension) | **~ 0.8 ml** | **~ 1.0 ml** | **~ 0.7 ml** | **~ 0.8 ml** | **~ 1.2 ml** |
| Sedimentation Volume at ~3 min (of 5 ml suspension) | **~ 1.5** | **~ 2.7** | **~ 4.7** | **~ 1.5** | **~ 3.6** |
| Syringeability at ~ 48 h - 27 Gauge needle, 1 cc. Syringe | **Pass** | **Pass** | **Pass** | **Pass** | **Pass** |
| Absorbance$_{245\,nm}$ > 48 h in supernatant (100x dilution) | **0.483** | **0.431** | **0.477** | **0.465** | **0.678** |
| Dose Accuracy with 27 gauge needle, 1cc syringe | **95.4%** | **95.8%** | **99.3%** | **87.5%** | **97.1%** |
| Microscopy | **~ 2–10μ** | **~ 2–10μ** | **~ 2–10μ** | **~ 2–10μ** | **~ 2–10μ** |

__Example 6:__ **Pharmacokinetic Study of Mg diparecoxib, parecoxib free acid, and valdecoxib compositions in Dogs.**

**[000127]** The above-recited suspensions were injected in dogs and serum levels of valdecoxib were measured at the times indicated in Table VI and Figure 8.

**Table VI**

| Time | Averaged Valdecoxib Plasma Level (ng/ml) [ n=3 dogs ] | | |
|---|---|---|---|
| Hours | parecoxib FA | Mg diparecoxib | valdecoxib |
| 0.000 | 0.0 | 0.0 | 0.0 |
| 0.167 | 18.6 | 14.2 | 54.4 |
| 0.500 | 228.0 | 94.8 | 107.0 |
| 1.000 | 582.0 | 180.0 | 139.0 |
| 2.000 | 673.0 | 348.0 | 192.0 |
| 3.000 | 323.0 | 404.0 | 187.0 |
| 6.000 | 121.0 | 168.0 | 95.4 |
| 12.000 | 50.8 | 84.8 | 51.2 |
| 24.000 | 36.1 | 99.4 | 70.4 |
| 36.000 | 8.9 | 26.6 | 30.9 |
| 48.000 | 4.1 | 39.7 | 55.2 |
| 60.000 | 0.5 | 12.5 | 20.7 |
| 72.000 | 0.0 | 14.6 | 46.4 |
| 84.000 | 0.0 | 1.4 | 18.5 |
| 96.000 | 0.0 | 0.8 | 45.2 |
| 108.000 | 0.0 | 0.0 | 12.9 |
| 120.000 | 0.0 | 0.0 | 17.5 |

**[000128]** When the data from this same study was subjected to deconvultion and expressed as cumulative input rate, it can be seen (Figure 9) that Mg diparecoxib has a linear rate of release for at least 100 hours. This is in stark contrast to valdecoxib and parecoxib free acid which show that after about 25 hours and 75 hours respectively, little or no additional valdecoxib is released into the blood. This is a surprising and unexpected result in view of the in vitro solubilization data of Figure 1 and Table IV that showed near maximal solubilization of Mg diparecoxib by 20 hours and roughly linear solubilization for valdecoxib from the period between one hour and 89 hours. Moreover, in vitro solubilzation of Na parecoxib showed a linear profile, but at a rate nearly 1/10$^{th}$ that of Mg diparecoxib.

**Example 7: Pharmacokinetic Study of Mg diparecoxib composition in Dogs.**

**[000129]** The objectives were to scale up the selected Mg diparecoxib composition to 1 liter scale and manufacture it with aseptic technique for a pharmacokinetic study in dogs. A batch of approx 1 liter of Mg diparecoxib was manufactured and filled in depyrogenated USP Type-I glass vials. The parecoxib salt concentration was

equivalent to approx 40 mg/ml Parecoxib free acid. Physico-chemical testing was conducted after manufacture (T=0 timepoint). The composition composition and a summary of the characterization results is provided in Table VII. The composition had almost 99% of the parecoxib in suspension form, with an average particle size of approx 40 microns. The suspension was redispersable and syringeable, and also passed tests for sterility and endotoxin.

**Table VII. Characterization of 1 Liter Batch of Mg diparecoxib**

| | |
|---|---|
| Composition | 40 mg/ml Mg diparecoxib<br>10 mM Tris Hydrochloride<br>5% Mannitol<br>Magnesium Chloride ~5mM<br>Sodium Chloride, ~100mM (formed in-situ by addition of $MgCl_2$ reagent to Na parecoxib |
| Batch Size | 1000 ml |
| Appearance | White homogenous suspension when mixed |
| Redispersability<br>(# of vial inversions) | 6 |
| Syringeability with 23 gauge needle and 1cc syringe | Pass<br>(also passed with 27 gauge needle) |
| *Average Particle Size by Horiba Sizer (microns) | Estimated at approx 40 microns<br>Approx 20 microns with 1 min Sonication |
| *Total Content by HPLC (%) | 103.3 ± 0.8 |
| *Supernatant Content (HPLC) | 0.48 mg/ml |
| *Test of Sterility | Pass |
| *Endotoxin | Pass |

a.

[000130] Composition vials were also stored at different temperature conditions for an informal stability evaluation. The analytical results indicated that the composition was stable at room temperature for at least 4 weeks.

[000131] The composition was successfully administered to dogs by intramuscular injection. Plasma levels of parecoxib and its active metabolite valdecoxib were monitored up to four days. Significant plasma concentrations of valdecoxib were

observed for at least 3 days from the Mg diparecoxib suspension composition as shown in Figure 10. For comparison, a simulated pharmacokinetic profile from an equivalent dose of Na parecoxib given intravenously is also shown.

**Example 8. Simulated Human Plasma Concentration – Time profiles for Mg diparecoxib**

**[000132]** Human plasma concentration of valdecoxib were simulated based upon dog pharmocokinetic analyses. Similar absorption rate for humans as observed in dogs. If absorption is strictly blood / plasma flow dependent, plasma levels may be 10 – 50% lower. Half life of Valdecoxib is ~ 1.4 hours in dogs versus ~ 7.4 hours in humans. Minimum therapeutic concentration of Valdecoxib is approx 50 ng/ml in humans (from PK studies with oral Valdecoxib). Such simulation is shown in Figure 11.

## WHAT IS CLAIMED IS:

1. A compound having the structure $MgX^1X^2$, wherein $X^1$ is parecoxib anion and $X^2$ is selected from the group consisting of parecoxib anion and another pharmaceutically acceptable anion.

1.1 The compound of Claim 1 wherein the at least one pharmaceutically acceptable anion is selected from the group consisting of chloride, bromide, sulfate, phosphate, nitrate, acetate, propionate, succinate, glycolate, stearate, lactate, malate, tartrate, citrate, ascorbate, glutamate, benzoate, salicylate, methanesulfonate, and toluenesulfonate.

2. The compound of Claim 1 substantially in the form of diparecoxib magnesium.

2.1 The compound of Claim 2 wherein the molar ratio of parecoxib anion to Mg cation is at least about 1.5 and equal to or less than about 2.5.

3. The compound of Claim 2 in the form of a crystal.

3.1 The compound of Claim 1 wherein the crystals have an average particle size of less than about 100 microns as determined by a Horiba Particle Sizer.

3.2 The compound of Claim 1 wherein the crystals have an average particle size of about 40 microns as determined by a Horiba Particle Sizer.

3.2 The compound of Claim 1 wherein the crystals have an average particle size of less than about 20 microns as determined by a Horiba Particle Sizer.

4. The compound of Claim 3 wherein the crystals are cuboidal or polygonal.

5. The compound of Claim 3 wherein the crystal has a surface to volume ratio less than about 48 microns $^{-1}$.

6. The compound of Claim 3 wherein the crystal has a surface to mass volume less than about 24 microns $^{-1}$.

7. The compound of Claim 3 wherein the crystal has a surface to volume ratio less than about 12 microns $^{-1}$.

8. A dosage form comprising the compound of Claim 1.

9. The dosage form of Claim 8 further comprising at least one excipient.

10. The dosage form of Claim 8 wherein the excipient comprises at least one agent selected from the group consisting of an anti-oxidant, a preservative, and a moldable agent.

10.1 The dosage form of Claim 8 comprising Mg diparecoxib in an amount at least about 1% by weight of the total dosage form.

10.2 The dosage form of Claim 8 comprising Mg diparecoxib in an amount at least about 10% by weight of the total dosage form.

10.3 The dosage form of Claim 8 comprising Mg diparecoxib in an amount at least about 20% by weight of the total dosage form.

11. The dosage form of Claim 8 in a form selected from the group consisting of a pill, a tablet, a capsule, a solution, and a suspension.

12. The dosage form of Claim 8 in the form of a suspension.

13. The dosage form of Claim 12 further comprising at least one member of the group consisting of a suspending agent and a isotonicity agent.

13.1 The dosage form of Claim 13 wherein the isotonicity agent, if present, comprises at least one agent selected from the group consiting of NaCl, a sorbitol, a mannitol, a dextrose, a polyethylene glycol, a phosphate buffer, a paraben, a propyl paraben, a carboxymethylcellulose, an alginate, a polyvinyl pyrrolidone, and a polysorbate.

13.2 The dosage form of Claim 13 further comprising a buffering agent.

13.3. The dosage form of Claim 13.2 wherein the buffer maintains the dosage form to a pH suitable for *in vivo* administration.

14. The dosage form of Claim 8 suitable for injection into at least one parenteral site.

15. The compound of Claim 14 wherein the at least one parenteral site is selected from the group of sites consisting of intradermal, intramuscular, intrat-articular, intraperitoneal, intralymphoid, subcutaneous, and subdural.

16 The dosage form of Claim 15 wherein, upon injection into the at least one parenteral site, the dosage form provides at least one of:

(a) a therapeutic level of valdecoxib within about 5 hours after injection;

(b) a therapeutic level of valdecoxib for at least about 3 days after injection; and

(c) a time to reach one half maximum blood serum concentration of valdecoxib not greater than about 10 hours after injection.

17. The dosage form of Claim 14 wherein upon injection into the at least one parenteral site, said compound is released from said parenteral site over a sustained period of time.

18. The dosage form of Claim 17 wherein the sustained period of time is at least about two days.

19. The dosage form of Claim 17 wherein the sustained period of time is at least about three days.

20. The dosage form of Claim 17 wherein the sustained period of time is at least about four days.

21. The dosage form of Claim 17 wherein therapeutic serum levels of the compound are achieved in the subject during said sustained period of time.

22. The dosage form of Claim 8 further comprising a second therapeutic agent.

23. The dosage form of Claim 22 wherein the second therapeutic agent is selected from the group consisting of an analgesic agent, an anti-pyretic agent, and an anti-inflammatory agent.

24. The dosage form of Claim 22 wherein the second therapeutic agent is selective from the group consisting of valdecoxib and a valdecoxib prodrug.

25. The dosage form of Claim 24 wherein the compound and the second therapeutic agent are each present in absolute and relative amounts wherein if the dosage form is administered to a subject in need thereof, then levels of circulating valdecoxib are sustained above a therapeutic level for said subject for at least about two days.

26. A method of making the compound of Claim 1 comprising the step of (a) dissolving parecoxib free acid or sodium parecoxib in an aqueous solvent; (b) adding a magnesium salt; (c) providing a period of time to allow precipitation of the compound; and (d) isolating the compound.

27. The compound of Claim 1 made by *in situ* crystallization.

28. The compound of Claim 1 made by reacting parecoxib free acid with a Mg salt.

29. A method for providing a long acting selective COX-2 inhibitory effect comprising injecting into a subject an amount of the composition of Claim 14 sufficient to produce said long acting selective COX-2 inhibitory effect.

101. A compound having the structure Ca $X^1X^2$ wherein $X^1$ is parecoxib anion and $X^2$ is selected from the group consisting of parecoxib anion and another pharmaceutically acceptable anion.

102. The compound of Claim 101 substantially in the form of diparecoxib calcium having a molar ratio of parecoxib anion to Ca cation of at least about 1.5 and less than or equal to about 3.

103. The compound of Claim 101 in the form of crystals.

104. The compound of Claim 103 wherein the crystals are needle-like in shape.

111. A compound having the structure Zn $X^1X^2$ wherein $X^1$ is parecoxib anion and $X^2$ is selected from the group consisting of parecoxib anion and another pharmaceutically acceptable anion.

112. The compound of Claim 111 substantially in the form of Zn diparecoxib having a molar ratio of parecoxib to Zn of at least about 1.5 and less than or equal to about 3.

113. The compound of Claim 201 in the form of a crystal.

121. A compound having the structure K $X^1$ wherein $X^1$ is a parecoxib anion.

122. The compound of Claim 121 substantially in the form of K parecoxib having a molar ratio of parecoxib anion to K cation of at least about 1.5 and less than or equal to about 3.

123. The compound of Claim 121 in the form of a crystal.

131. A dosage form comprising valdecoxib and an excipient wherein said dosage form is suitable for depot administration.

132. A dosage form comprising Na parecoxib and an excipient wherein said dosage form is suitable for depot administration.

141. A dosage form comprising the compound of any of Claims 101, 111, 121, or 131.

142. The dosage form of Claim 141 wherein upon depot administration, said compound is released from a site of said depot administration over a sustained period of time.

Figure 1

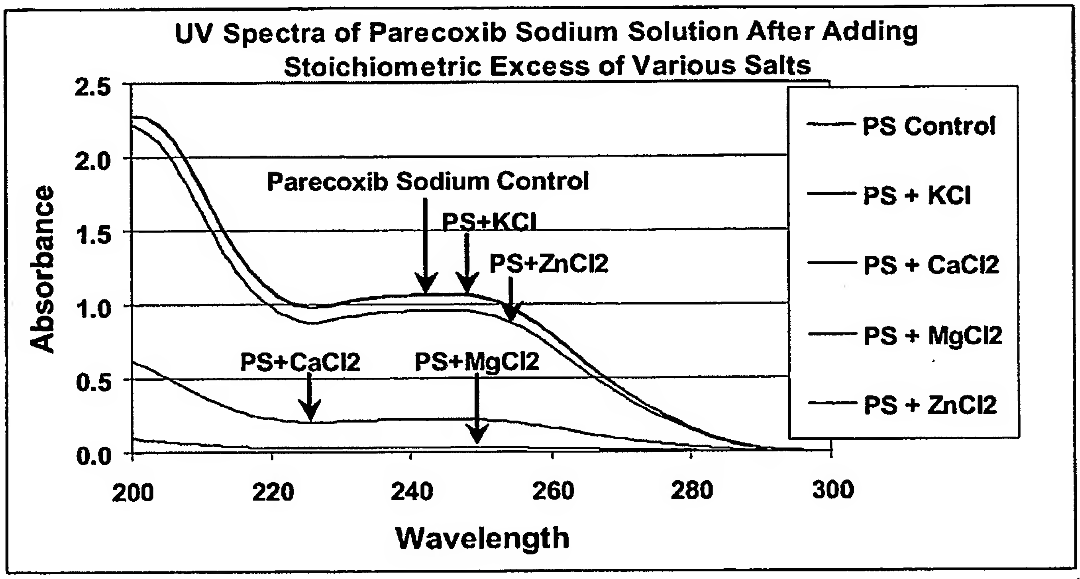



Figure 2

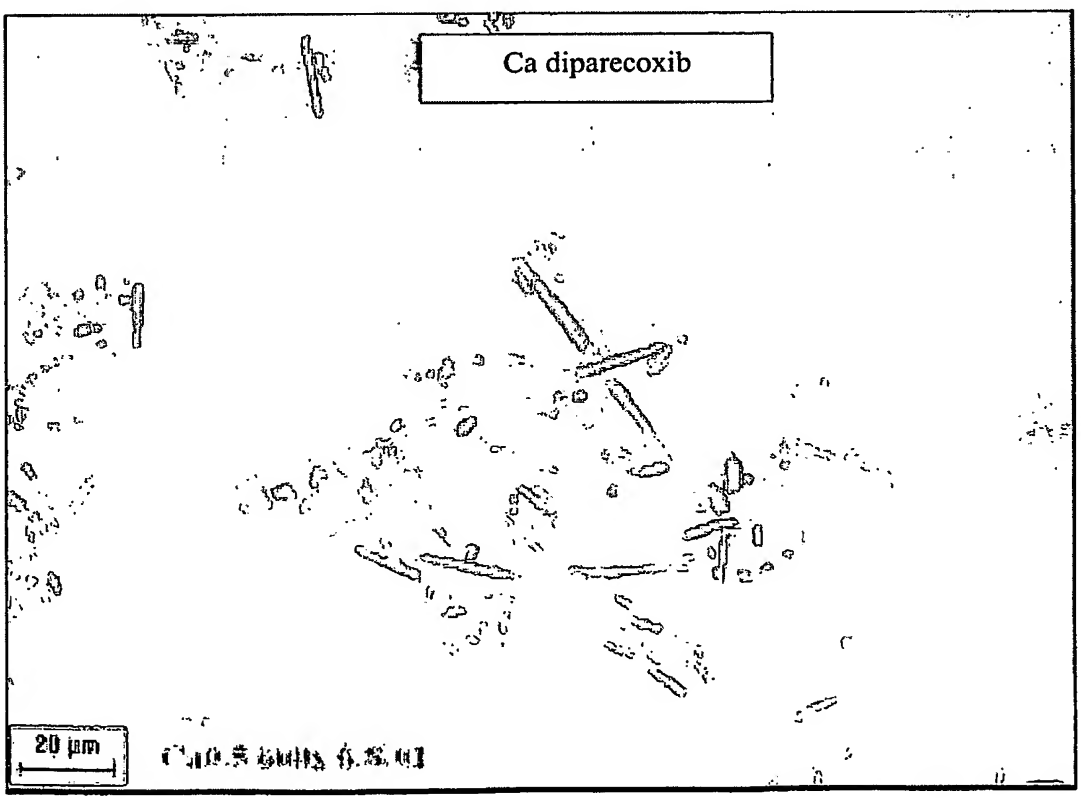


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Figure 3

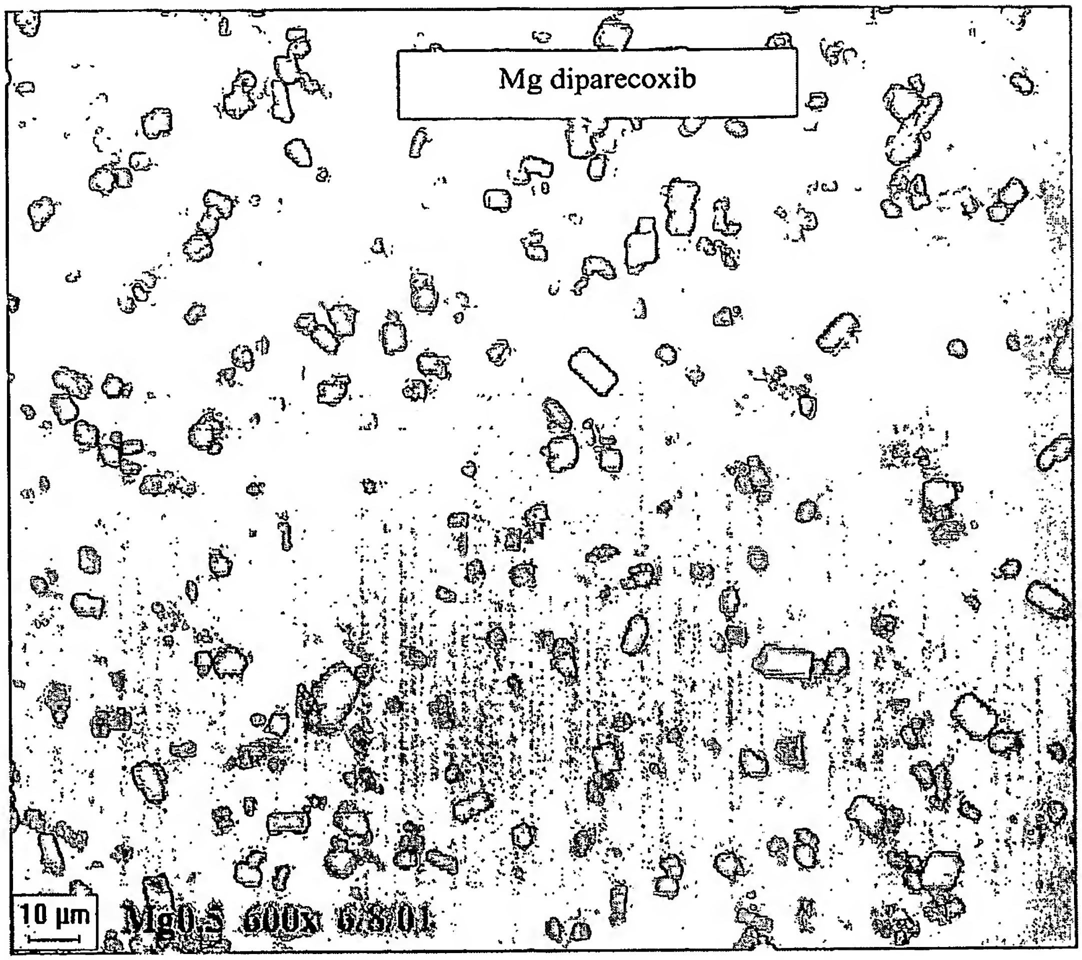

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Figure 4

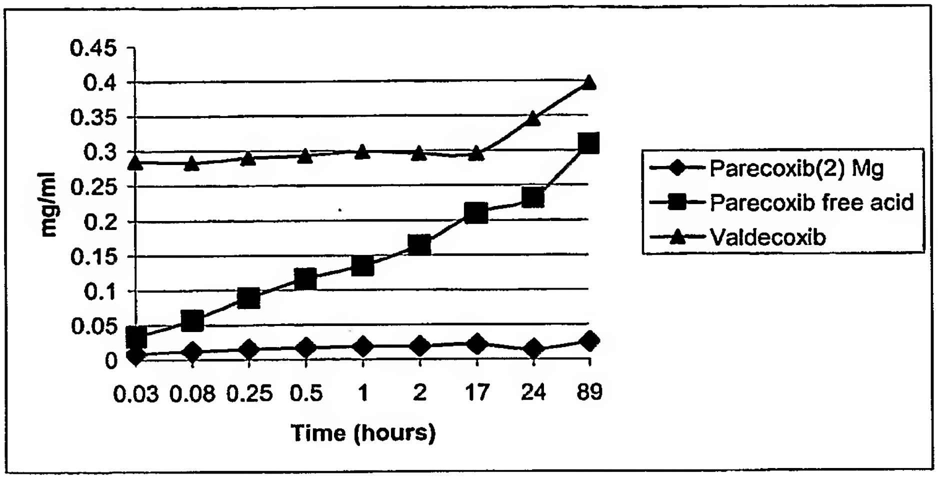

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Figure 5: Parecoxcib free acid

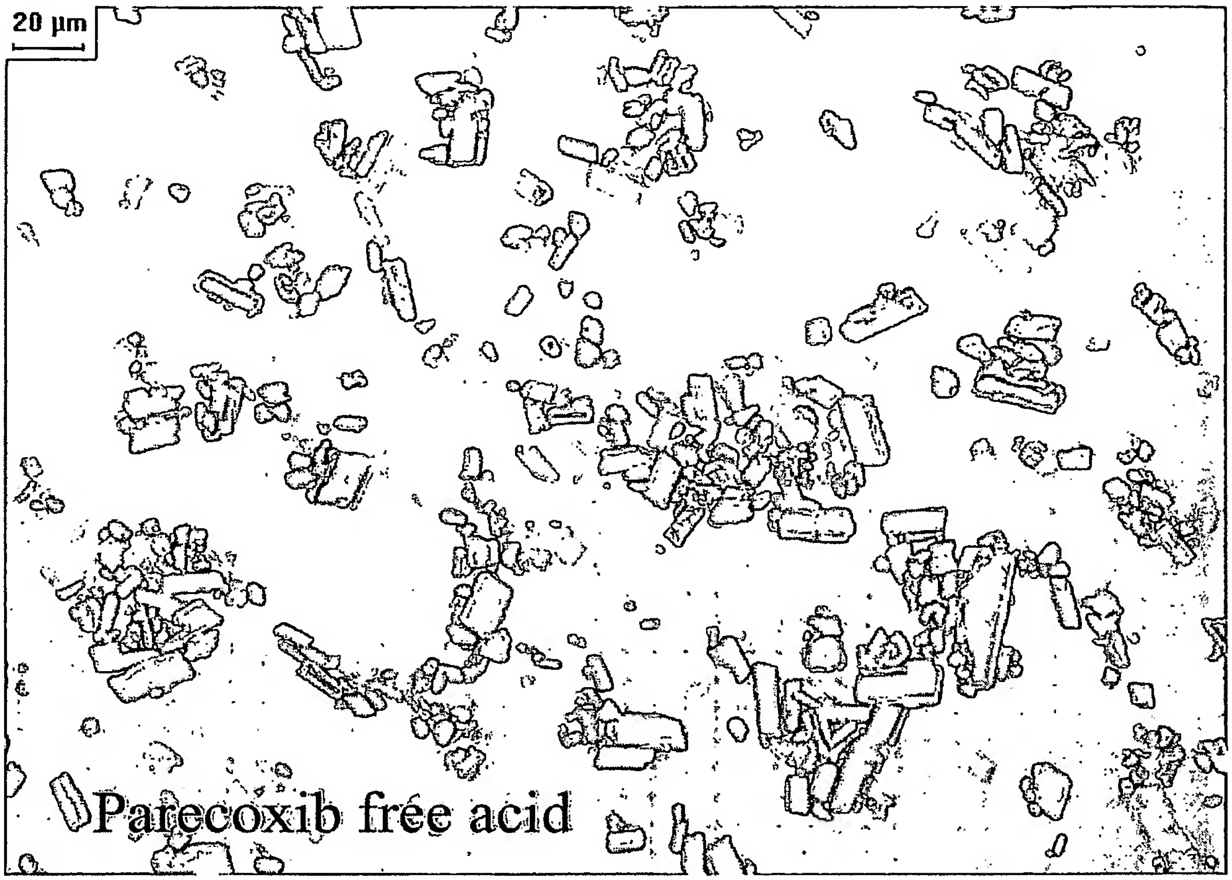

Figure 6 : Mg diparecoxib.

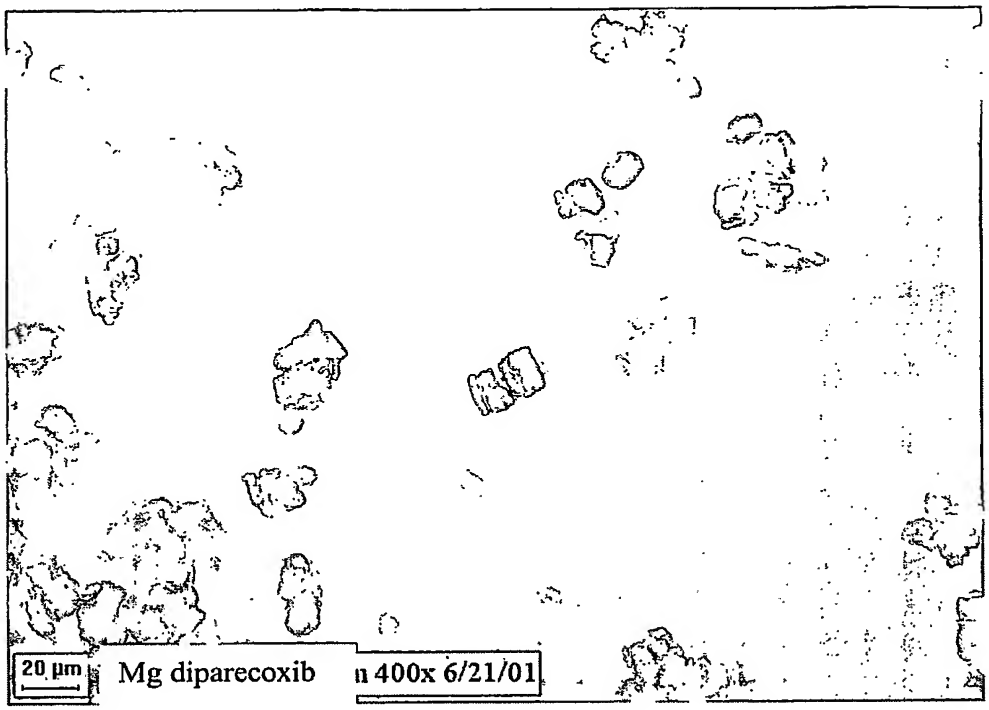

Figure 7

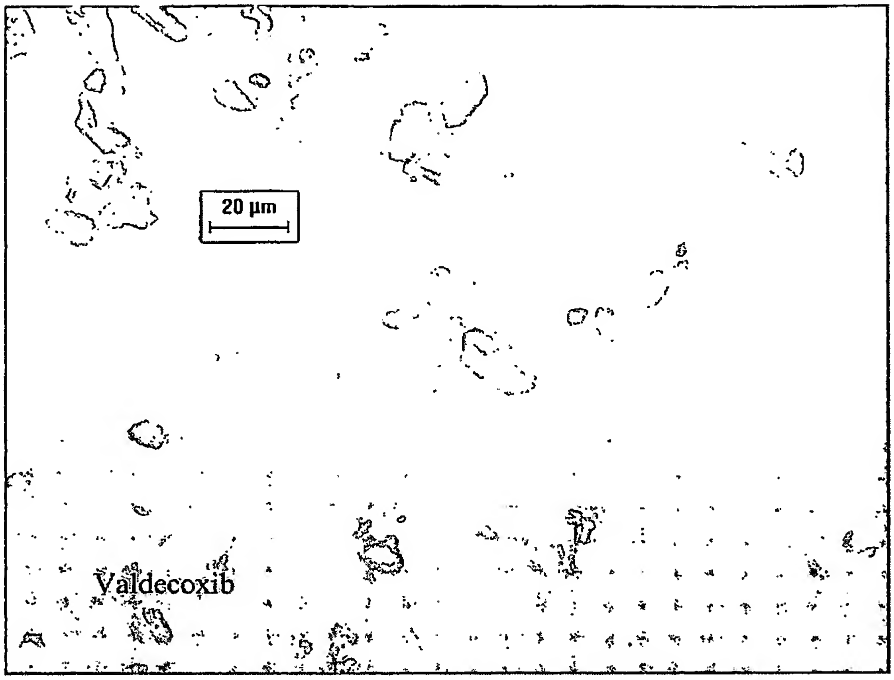

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Figure 8

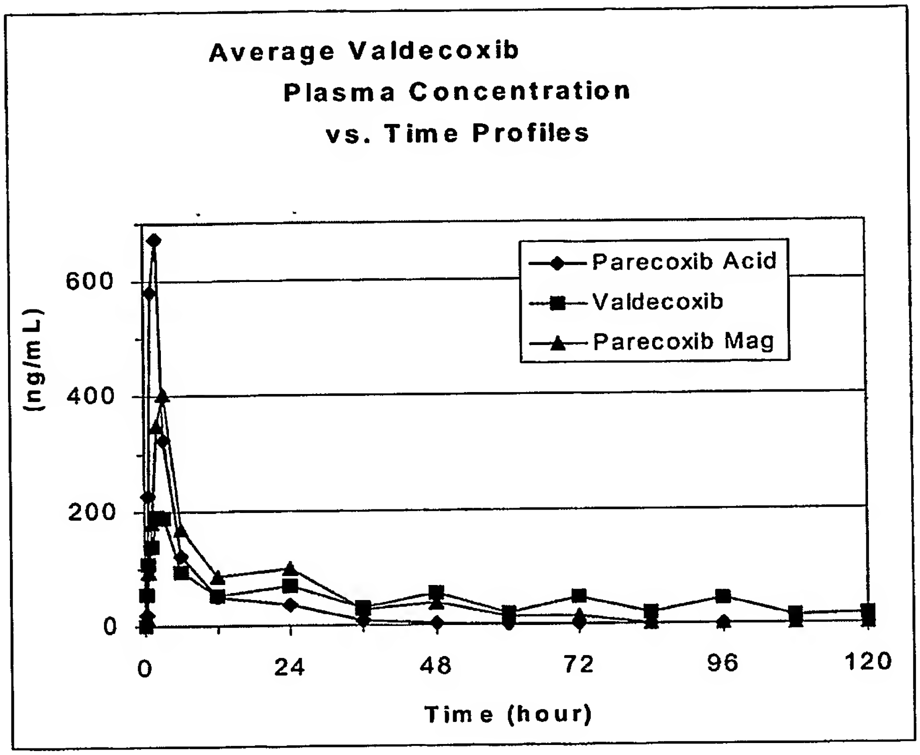
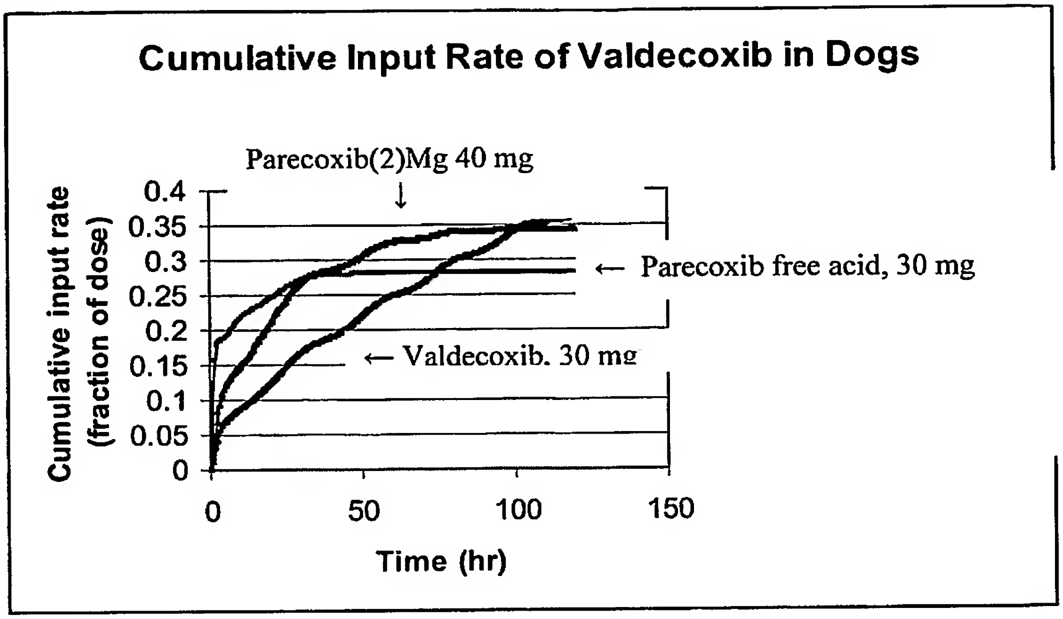


Figure 9:


Cumulative Input Rate of Valdecoxib in Dogs
Parecoxib(2)Mg 40 mg
Parecoxib free acid, 30 mg
Valdecoxib. 30 mg
Cumulative input rate (fraction of dose)
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
0
50
100
150
Time (hr)

00931/1

Figure 10

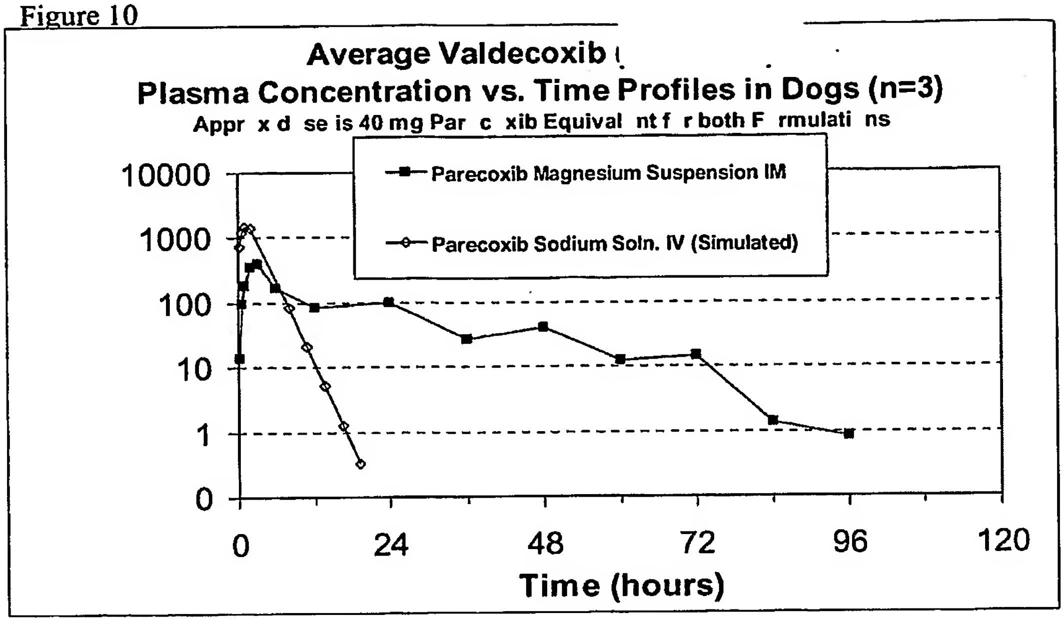
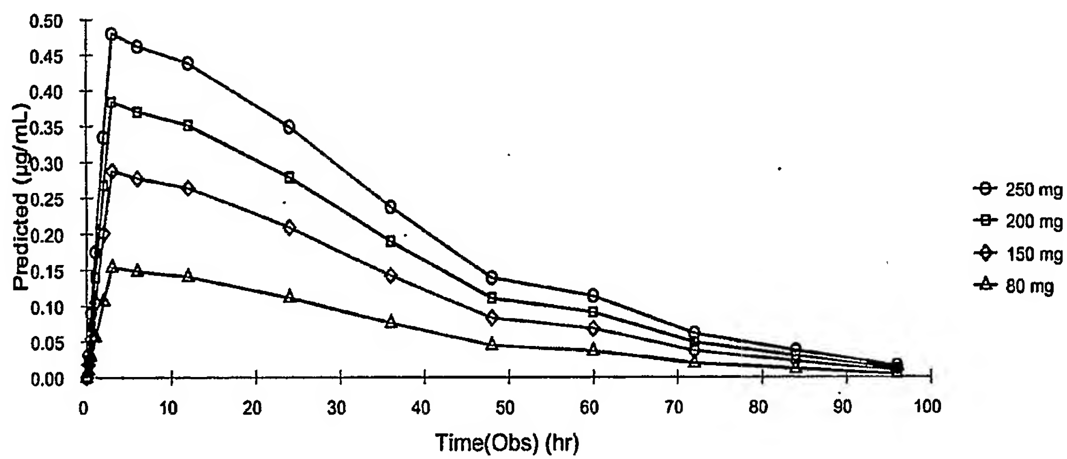


Figure 11.



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0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
Predicted (µg/mL)
0
10
20
30
40
50
60
70
80
90
100
Time(Obs) (hr)
250 mg
200 mg
150 mg
80 mg

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